(FILE 'HOME' ENTERED AT 15:01:19 ON 07 AUG 2000)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:01:30 ON 07 AUG 2000

```
L1       727346 S ADEPT OR ADC OR PRODRUG OR TARGET?
L2        47633 S FUSION PROTEIN
L3         6428 S L1 AND L2
L4          572 S CARBOXYESTERASE OR CPG2
L5           14 S L4 AND L3
L6            6 DUP REM L5 (8 DUPLICATES REMOVED)
L7        41270 S CEA OR CARCINOEMBRYONIC
L8           62 S L3 AND L7
L9         2666 S CAMPOTHECIN OR CPT-11
L10           0 S L8 AND L9
L11           0 S L9 AND L3
L12     1055000 S INFECTIOUS OR PARASIT? OR CLOT OR INFARCTION OR
ATHEROSCLERO?
L13         194 S L3 AND L12
L14     9209339 S THERAP? OR TREAT?
L15          55 S L14 AND L13
L16          31 DUP REM L15 (24 DUPLICATES REMOVED)
L17         189 S CLEARING AGENT
L18           0 S L17 AND L8
L19          77 S L17 AND L14
L20          30 S L19 AND L1
L21          18 DUP REM L20 (12 DUPLICATES REMOVED)
L22          31 DUP REM L8 (31 DUPLICATES REMOVED)
L23          81 S L6 OR L22 OR L21 OR L16
L24          81 DUP REM L23 (0 DUPLICATES REMOVED)
L25       23031 S IDIOTYPIC
L26           1 S L25 AND L17
L27        1597 S ((HANSEN H.J.) OR (HANSEN H J) OR (HANSEN, HANS J.) OR
(HANSE
L28          73 S L27 AND L1 AND L14
L29           7 S L28 AND L17
L30           4 DUP REM L29 (3 DUPLICATES REMOVED)
L31           1 S L9 AND L27 AND L1
L32          82 S L24 OR L30 OR L31
L33          82 DUP REM L32 (0 DUPLICATES REMOVED)
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L33 ANSWER 1 OF 82 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 2000:209950 CAPLUS
DOCUMENT NUMBER: 132:241926
TITLE: Methods and compositions for increasing the ***target*** -specific toxicity of a chemotherapy drug
INVENTOR(S): Griffiths, Gary L.; ***Hansen, Hans J.***
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000016808	A2	20000330	WO 1999-US21308	19990917

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,

MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9961475 A1 20000410 AU 1999-61475 19990917
PRIORITY APPLN. INFO.: US 1998-101039 19980918
WO 1999-US21308 19990917

AB A method for increasing the ***target*** -specific toxicity of a drug is effected by pretargeting an enzyme to a mammalian ***target*** site, and then administering a cytotoxic drug known to act at the ***target*** site, or a ***prodrug*** form thereof which is converted to the drug in situ, which drug is also detoxified to form an intermediate of lower toxicity using said mammal's ordinary metabolic processes, whereby the detoxified intermediate is reconverted to its more toxic form by the pretargeted enzyme and thus has enhanced cytotoxicity at the ***target*** site. Further enhancement can be achieved by pretargeting an enzyme which converts the ***prodrug*** to the cytotoxic drug at the ***target*** site. Kits for use with the method also are provided. The method and kits permit lower doses of cytotoxic agents, maximize ***target*** site activity and minimize systemic side effects.

L33 ANSWER 2 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:84648 CAPLUS
DOCUMENT NUMBER: 132:141941
TITLE: Conjugates and fusion proteins for ***treating*** secondary tissue damage and other inflammatory conditions and disorders
INVENTOR(S): Mcdonald, John R.; Coggins, Philip J.
PATENT ASSIGNEE(S): Osprey Pharmaceuticals Limited, Can.
SOURCE: PCT Int. Appl., 204 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000004926	A2	20000203	WO 1999-CA659	19990721

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9948918 A1 20000214 AU 1999-48918 19990721
PRIORITY APPLN. INFO.: US 1998-120523 19980722
WO 1999-CA659 19990721

AB Conjugates contg. as a ligand a chemokine receptor- ***targeting*** agent, such as chemokines, and a ***targeted*** agent, such as a toxin

are provided. These conjugates are used to ***treat*** inflammatory responses assocd. with activation, proliferation and migration of immune effector cells, including leukocyte cell types, neutrophils, macrophages, and eosinophils. The conjugates provided herein are used to lessen or inhibit these processes to prevent or at least lessen the resulting secondary effects. In particular, the conjugates are used to ***target*** toxins to receptors on secondary tissue damage-promoting cells. The ligand moiety can be selected to deliver the cell toxin to such secondary tissue damage-promoting cells as mononuclear phagocytes, leukocytes, natural killer cells, dendritic cells, and T and B lymphocytes, thereby suppressing the proliferation, migration, or physiol. activity of such cells. Among preferred conjugates are fusion proteins having a chemokine, or a biol. active fragment thereof, as the ligand moiety linked to a cell toxin via a peptide linker of from 2 to about 60 amino acid residues.

L33 ANSWER 3 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:285632 CAPLUS
DOCUMENT NUMBER: 132:320944
TITLE: Antibody to cytokine response gene 2 (CR2) polypeptide
INVENTOR(S): Smith, Kendall A.; Beadling, Carol
PATENT ASSIGNEE(S): Trustees of Dartmouth College, USA
SOURCE: U.S., 66 pp., Cont.-in-part of U.S. 5,795,752.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6057427	A	20000502	US 1996-652446	19960605
US 5795752	A	19980818	US 1994-330108	19941027
PRIORITY APPLN. INFO.:			US 1991-796066	19911120
			US 1993-104736	19930810
			US 1994-330108	19941027
			WO 1996-US8992	19960605

AB Disclosed are an isolated antibody or antibody fragment that selectively binds a polypeptide encoded by Cytokine Response gene 2 (CR2), and in particular, selectively binds to a first polypeptide having the sequence of residues 1-60 of SEQ. ID. No: 4. Also disclosed is a compn. contg. the antibody or antibody fragment and a diluent or carrier. Also disclosed are methods, using the present antibody or antibody fragment, of isolating or purifying a peptide comprising an amino acid sequence of residues 1-60 of SEQ. ID. No: 4 or an antibody binding fragment thereof that is at least 10 to 30 amino acids long, or a ***fusion*** ***protein*** comprising any of these. The invention also relates to the cytokine response gene CR1, CR3, CR5, CR6, CR7 and CR8; DNA and RNA probes; and ***fusion*** ***protein*** comprising CR2 fragment and polymerase activating peptide, c-raf, c-fos, c-myc, c-myb, pim-1 or other antigen peptide. The genes and polypeptides of the invention may be used as diagnostic or ***therapeutic*** agents for cancer, immunol. disease, allergy, autoimmune disease, rheumatol. disease, transplant rejection, anti-infective agent for viral, bacterial, ***parasitic*** and fungal infections, and as ***targets*** for the development of assays for

new
drug discovery.
REFERENCE COUNT: 6
REFERENCE(S): (1) Abdollahi, A; Oncogene 1991, V6, P165 CAPLUS
(2) Dickinson, L; Cell 1992, V70, P631 CAPLUS
(3) Regan, J; Molec Pharmacol 1994, V46, P213 CAPLUS
(5) Siderovski, D; DNA and Cell Biology 1994, V13(2), P125 CAPLUS
(6) Yoshimura, A; The EMBO Journal 1995, V14(12), P2816 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 4 OF 82 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:264587 BIOSIS
DOCUMENT NUMBER: PREV200000264587
TITLE: In-vivo characteristics of a glycosylated ***fusion*** ***protein*** for ***prodrug*** activation.
AUTHOR(S): Sharma, Surinder Kanta (1); Pedley, R. Barbara; Bhatia, Jeetendra; Minton, Nigel; Chester, Kerry A.; Begent, Richard Hj.
CORPORATE SOURCE: (1) Camr, Porton Down UK
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (March, 2000) No. 41, pp. 710. print.. Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California,
USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L33 ANSWER 5 OF 82 MEDLINE
ACCESSION NUMBER: 2000164576 MEDLINE
DOCUMENT NUMBER: 20164576
TITLE: Catalytic activity of an in vivo tumor ***targeted*** anti- ***CEA*** scFv::carboxypeptidase G2 ***fusion*** ***protein*** .
AUTHOR: Bhatia J; Sharma S K; Chester K A; Pedley R B; Boden R W; Read D A; Boxer G M; Michael N P; Begent R H
CORPORATE SOURCE: Department of Oncology, Royal Free and University College Medical School, London, UK.. jeet@rfhsm.ac.uk
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (2000 Feb 15) 85 (4) 571-7.
Journal code: GQU. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200005
ENTRY WEEK: 20000504
AB Antibody-directed enzyme ***prodrug*** therapy (***ADEPT***) ***targets*** an enzyme selectively to a tumor where it converts a relatively non-toxic ***prodrug*** to a potent cytotoxic drug. Previous clinical work using antibody-enzyme chemical conjugates has been limited by the moderate efficiency of tumor ***targeting*** of these molecules. To address this a recombinant ***fusion*** ***protein*** composed of MFE-23, an anti- ***carcinoembryonic*** antigen (

CEA) single chain Fv (scFv) antibody, fused to the amino-terminus of the enzyme carboxypeptidase G2 (***CPG2***) has been constructed to achieve ***ADEPT*** in ***CEA*** -producing tumors. MFE-23:: ***CPG2*** ***fusion*** ***protein*** was overexpressed in Escherichia coli and purified using ***CEA*** affinity chromatography. Efficacy of MFE-23:: ***CPG2*** delivery to tumors in vivo was assessed by measuring catalytic activity after intravenous injection of purified MFE-23:: ***CPG2*** into nude mice bearing ***CEA*** -positive LS174T human colon adenocarcinoma xenografts. Recombinant MFE-23:: ***CPG2*** cleared rapidly from circulation and catalytic activity in extracted tissues showed tumor to plasma ratios of 1.5:1 (6 hr), 10:1 (24 hr), 19:1 (48 hr) and 12:1 (72 hr). (125)I-MFE-23:: ***CPG2*** was retained in kidney, liver and spleen but MFE-23:: ***CPG2*** catalytic activity was not, resulting in excellent tumor to normal tissue enzyme ratios 48 hr after injection. These were 371:1 (tumor to liver), 450:1 (tumor to lung), 562:1 (tumor to kidney), 1,477:1 (tumor to colon) and 1,618:1 (tumor to spleen). Favorable tumor : normal tissue ratios occurred at early time points when there was still 21% (24 hr) and 9.5% (48 hr) of the injected activity present per gram of tumor tissue. The high tumor concentrations and selective tumor retention of active enzyme delivered by MFE-23:: ***CPG2*** establish that this recombinant ***fusion*** ***protein*** has potential to give improved clinical efficiency for ***ADEPT*** . Copyright 2000 Wiley-Liss, Inc.

L33 ANSWER 6 OF 82 MEDLINE
ACCESSION NUMBER: 2000210030 MEDLINE
DOCUMENT NUMBER: 20210030
TITLE: [Role of anti-TNF ***therapy*** in rheumatoid arthritis].
Place des ***therapeutiques*** anti-TNF dans la polyarthrite rhumatoide.
AUTHOR: Meyer O
CORPORATE SOURCE: Service de Rhumatologie, Hopital Bichat, Paris.. olivier.meyer@bch.ap-hop-paris.fr
SOURCE: PRESSE MEDICALE, (2000 Mar 11) 29 (9) 463-8. Ref: 50
Journal code: PMT. ISSN: 0755-4982.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200006
ENTRY WEEK: 20000604
AB TUMOR NECROSIS FACTOR: TNF is a cytokine produced by several types of cells, but mainly by monocyte-macrophages, activated endothelial cells, fibroblasts, and joint cartilage chondrocytes. The circulating form of TNF alpha (homotrimere) is derived from its membrane form by cleavage induced by a metalloprotease called TACE. This cytokine plays a pivotal role in the inflammatory reaction in conjunction with IL-1 and IL-6. The effect of TNF alpha is mediated by two membrane receptors carried on the surface of ***target*** cells (TNF-RI p55 and TNF-RII p75) which are released

into
the biological fluids (synovial fluid and plasma). ARGUMENTS FOR A PATHOGENIC ROLE: Transgenic mice carrying the human gene for TNF alpha develop polyarthritis suggesting this cytokine is directly implicated in the pathogenesis. In diverse cell types in rheumatoid joints, TNF alpha and its receptors can be identified by immunohistochemistry techniques as can TNF alpha mRNA by RT-PCR. ***THERAPEUTIC*** POSSIBILITIES: Anti-TNF alpha antibodies can effectively attenuate or prevent arthritis in the main experimental models. TNF alpha can also be neutralized with soluble receptors, TNF alpha RI or TNF alpha RII. The efficacy of these two ***therapeutics*** has been proven in rheumatoid arthritis, but with a short-term though remnant effect, leading to iterative injections and/or combinations with methotrexate. Short-term side effects are mild but the long-term ***infectious*** and oncogenic adverse effects remain to be determined. Is this simply a powerful antiinflammatory ***treatment*** or a real curative ***treatment*** ? A precise examination of radiographic scores will be required to provide the answer to this question.

L33 ANSWER 7 OF 82 MEDLINE
ACCESSION NUMBER: 2000142837 MEDLINE
DOCUMENT NUMBER: 20142837
TITLE: A recombinant antibody- ***targeted*** plasminogen activator with high affinity for activated platelets increases thrombolytic potency in vitro and in vivo.
AUTHOR: Wan H; Liu Z; Xia X; Gu J; Wang B; Liu X; Zhu M; Li P; Ruan C
CORPORATE SOURCE: Jiangsu Institute of Haematology, First Affiliated Hospital of Suzhou Medical College, People's Republic of China.
SOURCE: THROMBOSIS RESEARCH, (2000 Feb 1) 97 (3) 133-41. Journal code: VRN. ISSN: 0049-3848.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY WEEK: 20000503
AB To increase thrombolytic specificity of urokinase (uPA), we engineered a recombinant chimeric plasminogen activator SZ51Hu-scuPA, which consists of a humanized monoclonal antibody (SZ-51Hu) specifically against P-selectin on activated human platelet and a single-chain urokinase (scuPA). The cDNA, encoding scuPA amino acids 1-411, was inserted in 5' end to 3' end orientation immediately after the CH3 of SZ-51Hu heavy-chain sequence in the expression vector alphaLys30. The resulting construct alphaLys30-SZ51VH/Hu-scuPA was used to transfect into SP2/0 murine myeloma cell line, which was pretransfected with SZ51Hu light chain. The ***fusion*** ***protein*** SZ51Hu-scuPA was expressed at 5 mg/L in the supernatant of cell culture. The ***fusion*** ***protein*** purified by affinity chromatography had a molecular weight of 160 kDa with fibrinolytic activity of 39,000 IU/mg and its affinity to activated human platelet was 67% of the parent murine mAb SZ-51. The thrombolytic property of the ***fusion*** ***protein*** was first characterized in an in

vitro system, which consists of a 125I-fibrin-labeled human plasma ***clot*** containing different concentrations of human platelets suspended in citrated human plasma. Fifty percent lysis was reached with SZ51Hu-scuPA in 1 hour at a concentration of 20 IU/mL or in 2 hours at a concentration of 10 IU/ mL, which was much faster than uPA at the same concentration. The maximal lysis of the clots by SZ51Hu-scuPA was 4.1 to 8.4 times more potent than that by uPA. The ***fusion*** ***protein*** was further characterized in the hamster pulmonary embolism model with clots prepared from fresh platelet-rich human plasma containing 125I-labeled fibrinogen. The thrombolytic activity of SZ51-scuPA was 3.9 times more potent than that of uPA at 2,000 IU/kg in this model. Almost no significant fibrinogen breakdown was observed either in vitro and in vivo.

L33 ANSWER 8 OF 82 MEDLINE
ACCESSION NUMBER: 2000112142 MEDLINE
DOCUMENT NUMBER: 20112142
TITLE: Clinical optimization of pretargeted radioimmunotherapy with antibody-streptavidin conjugate and 90Y-DOTA-biotin.
AUTHOR: Breitz H B; Weiden P L; Beaumier P L; Axworthy D B; Seiler C; Su F M; Graves S; Bryan K; Reno J M
CORPORATE SOURCE: Department of Radiology, Virginia Mason Medical Center, Seattle, Washington, USA.
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (2000 Jan) 41 (1) 131-40. Journal code: JEC. ISSN: 0161-5505.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200004
ENTRY WEEK: 20000404
AB Pretargeted radioimmunotherapy (PRIT) was evaluated using an antibody-streptavidin conjugate, followed by a biotin-galactose-human serum albumin ***clearing*** ***agent*** and 90Y-dodecane tetraacetic acid (DOTA)-biotin as the final step for ***therapy*** . The objective was to develop a clinical protocol that could show an improved tumor-to-red marrow ***therapeutic*** ratio compared with conventional radioimmunotherapy (RIT) and at the same time preserve the efficiency of tumor ***targeting*** . METHOD: Forty-three patients with adenocarcinomas reactive to NR-LU-10 murine monoclonal antibody received the 3 components. Doses and timing parameters were varied to develop an optimized schema. In some patients, the conjugate was radiolabeled with 186Re as an imaging tracer to assess biodistribution of the conjugate and effectiveness of the ***clearing*** ***agent*** . 111In-DOTA-biotin was coinjected with 90Y-DOTA-biotin for quantitative imaging. Safety, biodistribution, pharmacokinetics, dosimetry, and antiglobulin formation were evaluated. RESULTS: The optimal schema was defined as a conjugate dose of 125 microg/mL plasma volume followed at 48 h by a ***clearing*** ***agent*** in a 10:1 molar ratio of ***clearing*** ***agent*** to serum conjugate. The ***therapeutic*** third step was 0.5 mg radiobiotin administered 24 h later. No significant adverse events were observed after administration of any of the components. The mean tumor-to-marrow absorbed dose ratio when using the optimized PRIT schema was 63:1, compared with a 6:1 ratio reported previously for conventional RIT. Antiglobulin to murine antibody and to streptavidin developed in most

patients. CONCLUSION: This initial study confirmed that the PRIT approach is safe and feasible and achieved a higher ***therapeutic*** ratio than that achieved with conventional RIT using the same antibody.

L33 ANSWER 9 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:65261 CAPLUS
DOCUMENT NUMBER: 132:249346
TITLE: Capsid- ***Targeted*** Viral Inactivation Can Eliminate the Production of ***Infectious*** Murine Leukemia Virus in Vitro
AUTHOR(S): VanBrocklin, Matthew; Federspiel, Mark J.
CORPORATE SOURCE: Molecular Medicine Program, Mayo Clinic and Mayo Foundation, Rochester, MN, 55905, USA
SOURCE: Virology (2000), 267(1), 111-123
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Capsid- ***targeted*** viral inactivation (CTVI), a promising gene-based antiviral strategy against retroviruses, was designed to disrupt the retroviral life cycle by incorporating a degradative enzyme (e.g., nuclease) into viral particles during assembly, thereby reducing or eliminating the prodn. of ***infectious*** virus. The exptl. system used to develop the CTVI strategy for retroviruses is designed to block the prodn. of ***infectious*** Moloney murine leukemia virus (Mo-MLV). Two nucleases, Escherichia coli RNase HI and Staphylococcus nuclease, have been shown to be tolerated by the cell as Mo-MLV Gag-nuclease fusion polyproteins and still be active in the viral particles. The goal of this study was to det. what cellular and viral factors limit CTVI in cultured cells. The avian DF-1 cell line greatly expanded our ability to test the antiviral efficacy of CTVI in long-term assays and to det. the mechanism(s) of CTVI action. The CTVI antiviral effect is dependent on the level of Mo-MLV Gag-nuclease fusion polyprotein expressed. The Mo-MLV Gag-nuclease polyproteins produce a long-term prophylactic antiviral effect after a low- or high-dose Mo-MLV challenge. The Mo-MLV Gag-nuclease fusions have a significant ***therapeutic*** effect (.apprx.1000-fold) on the prodn. of ***infectious*** Mo-MLV. The ***therapeutic*** CTVI effect can be improved by a second delivery of the CTVI fusion gene. Both the prophylactic and the ***therapeutic*** CTVI antiviral approaches can virtually eliminate the prodn. of ***infectious*** Mo-MLV in vitro and are only limited by the no. of cells in the population that do not express adequate levels of the CTVI fusion polyprotein. (c) 2000 Academic Press.
REFERENCE COUNT: 28
REFERENCE(S): (3) Bova, C; Virology 1986, V152, P343 CAPLUS
(4) Craven, R; Curr Top Microbiol Immunol 1996, V214, P65 CAPLUS
(5) Crouch, R; New Biolog 1990, V2, P771 CAPLUS
(6) Federspiel, M; Methods Cell Biol 1997, V52, P179 CAPLUS
(7) Federspiel, M; Virology 1994, V203, P211 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 10 OF 82 MEDLINE
ACCESSION NUMBER: 2000204822 MEDLINE

DOCUMENT NUMBER: 20204822
TITLE: Pretargeted radioimmunotherapy (PRIT) for ***treatment*** of non-Hodgkin's lymphoma (NHL): initial phase I/II study results [see comments].
COMMENT: Comment in: Cancer Biother Radiopharm 2000 Feb;15(1):1-5
AUTHOR: Weiden P L; Breitz H B; Press O; Appelbaum J W; Bryan J K; Gaffigan S; Stone D; Axworthy D; Fisher D; Reno J
CORPORATE SOURCE: Virginia Mason Medical Center, Seattle, WA, USA.
SOURCE: Cancer Biother Radiopharm, (2000 Feb) 15 (1) 15-29. Journal code: DLF. ISSN: 1084-9785.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY WEEK: 20000701

AB Pretargeted radioimmunotherapy (PRIT) was investigated in patients with non-Hodgkin's lymphoma (NHL). The PRIT approach used in this study is a multi-step delivery system in which an antibody is used to ***target*** streptavidin to a tumor associated antigen receptor, and subsequently biotin is then used to ***target*** 90Y radioisotope to the tumor localized streptavidin. A chimeric, IgG1, anti-CD20 antibody, designated C2B8 or Rituximab, was conjugated to streptavidin (SA) and administered to patients with NHL. Thirty-four hours later, a ***clearing*** ***agent*** , synthetic biotin-N-acetyl-galactosamine, was administered to remove non-localized conjugate from the circulation. Finally, a DOTA-biotin ligand, labeled with 111In for imaging and/or 90Y for ***therapy*** was administered. Ten patients with relapsed or refractory NHL were studied. In three patients, the C2B8/SA conjugate was radiolabeled with a trace amount of 186Re in order to assess pharmacokinetics and biodistribution using gamma camera imaging. Seven patients received 30 or 50 mCi/m2 90Y DOTA-biotin. Re-186 C2B8/SA images confirmed that the conjugate localized to known tumor sites and that the ***clearing*** ***agent*** removed > 95% of the conjugate from the circulation. Radiolabeled biotin localized well to tumor. Unbound radiobiotin was rapidly excreted from the whole body and normal organs. The mean tumor dose calculated was 29 +/- 23 cGy/mCi 90Y and the average whole body dose was 0.76 +/- 0.3 cGy/mCi 90Y, resulting in a mean tumor to whole body dose ratio of 38:1. Only grade I/II non-hematologic toxicity was observed. Hematologic toxicity was also not severe; i.e., five of the seven patients who received 30 or 50 mCi/m2 of 90Y-DOTA-biotin experienced only transient grade III (but no grade IV) hematologic toxicity. Although six of ten patients developed humoral immune responses to the streptavidin, these were delayed and transient and hence may not preclude retreatment. Six of seven patients who received 30 or 50mCi/m2 90Y achieved objective tumor regression, including three complete and one partial response. The estimate of tumor to whole body dose ratio (38:1) achieved with PRIT in these NHL patients is higher than has been achieved in other studies using conventional RIT. Toxicity was mild and tumor

response encouraging. PRIT clearly deserves additional study in patients with NHL.

L33 ANSWER 11 OF 82 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:291848 BIOSIS
DOCUMENT NUMBER: PREV200000291848
TITLE: Delivery of diagnostic and ***therapeutic*** agents to a ***target*** site.
AUTHOR(S): Griffiths, Gary L. (1); ***Hansen, Hans J.*** ; Govindan, Serengulam V.; Karacay, Habibe
CORPORATE SOURCE: (1) Clifton, NJ USA
ASSIGNEE: Immunomedics, Inc., Morris Plains, NJ, USA
PATENT INFORMATION: US 5965131 October 12, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 12, 1999) Vol. 1227, No. 2, pp. No pagination. e-file..
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB An improvement in in vivo pretargeting methods for delivering diagnostic or ***therapeutic*** agents to a ***target*** site in a mammal uses a ***clearing*** ***agent*** that binds to the ***target***
-binding site of the ***targeting*** species, whereby non-bound primary ***targeting*** species is cleared from circulation but the ***clearing*** ***agent*** does not remove the bound primary ***targeting*** species. Anti-idiotype antibodies and antibody fragments
are preferred clearing agents. Fast clearance is achieved by glycosylating
the ***clearing*** ***agent*** with sugar residues that bind to the hepatic asialoglycoprotein receptor.

L33 ANSWER 12 OF 82 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:10731 BIOSIS
DOCUMENT NUMBER: PREV200000010731
TITLE: Delivery of diagnostic and ***therapeutic*** agents to a ***target*** site.
AUTHOR(S): Griffiths, Gary L. (1); ***Hansen, Hans J.*** ; Govindan, Serengulam V.; Karacay, Habibe
CORPORATE SOURCE: (1) Morristown Memorial Hospital, Morristown, NJ USA
ASSIGNEE: Immunomedics, Inc.
PATENT INFORMATION: US 5958408 Sep. 28, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 28, 1999) Vol. 1226, No. 4, pp. No pagination.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

L33 ANSWER 13 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:736896 CAPLUS
DOCUMENT NUMBER: 132:2786
TITLE: Enhancing immune response to multiple CTL epitopes in fusion with a universal HTL epitopes and endoplasmic reticulum-translocating signal sequences from plasmid vector minigene and evaluating DNA vaccines in MHC class I transgenic mice
INVENTOR(S): Fikes, John D.; Hermanson, Gary G.; Sette, Alessandro;

Ishioka, Glenn Y.; Livingston, Brian; Chesnut, Robert W.
PATENT ASSIGNEE(S): Epimmune, Inc., USA
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958658	A2	19991118	WO 1999-US10646	19990513
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9940785	A1	19991129	AU 1999-40785	19990513
PRIORITY APPLN. INFO.:			US 1998-78904	19980513
			US 1998-85751	19980515
			WO 1999-US10646	19990513

AB A method of enhancing immune response to multiple CTL (cytotoxic T-cell) epitopes expressed from a plasmid vector by fusing them with a universal HTL (helper T-lymphocyte) epitope and reticulum-translocating signal sequences and evaluating DNA vaccines by using MHC class I transgenic mice was described. The prototype DNA vaccine (pMin.1)was derived from pcDNA3.1 and encoded nine dominant HLA-A2.1- and A11-restricted epitopes from the polymerase, envelope, and core proteins of hepatitis B virus and HIV. The coding sequences of PADRE (pan-DR epitope) universal Th cell epitope and an endoplasmic reticulum-translocating signal sequence (mouse IG.kappa. signal peptide) were fused with the coding sequence of the above nine CTL epitopes in the plasmid minigene to stimulate the immune response. Immunization of HLA transgenic mice with this construct resulted in: (1) simultaneous CTL induction against all nine CTL epitopes despite their varying MHC binding affinities; (2) CTL responses that were equiv. in magnitude to those induced against a lipopeptide known be immunogenic in humans; (3) induction of memory CTLs up to 4 mo after a single DNA injection; (4) higher epitope-specific CTL responses than immunization with DNA encoding whole protein; and (5) a correlation between the immunogenicity of DNA-encoded epitopes in vivo and the in vitro responses of specific CTL lines against minigene DNA-transfected ***target*** cells. Examn. of potential variables in minigene construct design revealed that removal of the PADRE Th cell epitope or the signal sequence, and changing the position of selected epitopes, affected the magnitude and frequency of CTL responses. It was demonstrated that the simultaneous induction of broad CTL responses in vivo against multiple dominant HLA-restricted epitopes using a minigene DNA vaccine was feasible and the utility of HLA transgenic mice in development and optimization of vaccine constructs for human use is an attractive alternative approach.

L33 ANSWER 14 OF 82 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:577005 CAPLUS
DOCUMENT NUMBER: 131:195448
TITLE: Delivery of proteins into eukaryotic cells with recombinant Yersinia
INVENTOR(S): Van Der Bruggen, Pierre B.; Cornelis, Guy R.; Boland, Anne M.; Boon-falleur, Thierry R.
PATENT ASSIGNEE(S): Belg.
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945098	A2	19990910	WO 1999-IB587	19990303
WO 9945098	A3	19991223		
W: AU, CA, CN, JP, KR, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5965381	A	19991012	US 1998-36582	19980306
AU 9928501	A1	19990920	AU 1999-28501	19990303
PRIORITY APPLN. INFO.:			US 1998-36582	19980306
			WO 1999-IB587	19990303

AB The present invention relates to recombinant Yersinia and the use thereof for delivery of proteins into eukaryotic cells, including related compns. and methods of ***treatment*** and related assays. Such Yersinia are deficient in the prodn. of functional effector proteins, but are endowed with a functional secretion and translocation system. To construct a yopHOPEM polymutant Yersinia strain, the yopE, yopH, yopO, yopM and yopP genes were successively knocked out by allelic exchange in the MRS40 strain using suicide vectors. A protein of a pathogenic origin, e.g., a tumor-assocd. protein, a ***parasite*** antigen, or a viral antigen, can be delivered using the recombinant Yersinia of the present invention into antigen-presenting cells for inducing an immune response specific for such a protein. Thus, a DNA sequence encoding MAGE-1 is inserted in frame with a sequence encoding a truncated YopE, YopE130, contg. the first 130 amino acids of YopE. Anti-MAGE-1.A1 cytotoxic lymphocytes recognize HLA-A1 cells incubated with Yersinia which produces a YopE130.MAGE-1 ***fusion*** ***protein*** .

L33 ANSWER 15 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:464299 CAPLUS
DOCUMENT NUMBER: 131:86867
TITLE: Expression of fusion proteins
INVENTOR(S): Hawkins, Robert Edward; Whittington, Hayley Ann
PATENT ASSIGNEE(S): University of Bristol, UK
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9936440	A2	19990722	WO 1999-GB152	19990118

WO 9936440 A3 19990916
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9921737 A1 19990802 AU 1999-21737 19990118
PRIORITY APPLN. INFO.: GB 1998-927 19980116
WO 1999-GB152 19990118

AB This invention provides a method of producing a ***fusion*** ***protein*** comprising an antibody portion and a further biol. active portion, the method comprising forming a virus-based construct including a DNA sequence encoding the ***fusion*** ***protein*** and infecting cells or an organism with the thus constructed virus-based construct whereby the ***fusion*** ***protein*** is expressed in in vitro in the cells, or in vivo in the organism. The virus-based construct is based on adenovirus, retrovirus, adeno-assocd. virus, herpes simplex virus or synthetic virus based particle; the antibody portion is derived from fragments of IgG1-4 or IgGE; and the biol. active portion is selected from cytokine, interferon, enzyme, toxin, cell surface ligand for cellular receptor. Thus, recombinant adenovirus was generated for expression of scFv.mGM-CSF and scFv-IL2 fusion proteins.

L33 ANSWER 16 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:468597 CAPLUS
DOCUMENT NUMBER: 131:101262
TITLE: Antibody/receptor ***targeting*** moiety for enhanced delivery of armed ligand
INVENTOR(S): Burton, Jack; Goldenberg, David M.
PATENT ASSIGNEE(S): Center for Molecular Medicine and Immunology, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9936437	A1	19990722	WO 1999-US773	19990114

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9922267 A1 19990802 AU 1999-22267 19990114
PRIORITY APPLN. INFO.: US 1998-71520 19980115

WO 1999-US773 19990114

AB A method for intracellular delivery of drugs or other agents for diagnosis and therapy of malignancies or immune-mediated or inflammatory conditions. A ***targeting*** moiety of an antibody and the ligand-binding region of a selected cytokine receptor is used. The ***targeting*** moiety ***targets*** surface antigen on a specific cell population. The ***targeting*** moiety is administered to a subject, and then, after a specified interval, therapeutic or diagnostic agents linked to the cognate cytokine are given. The invention provides rapid, efficient internalization of the cytokine receptor antibody/antigen complexes. ***Targeting*** of a high-level cell surface antigen with such bispecific fusion mols. substantially increases the no. of cytokine receptors over their low background level. Thus, bifunctional sol. ***fusion*** ***protein*** IL-13R.alpha.-MN-14scFv comprising interleukin 13 receptor .alpha. chain and anti- ***CEA*** antibody was prepd. and used with radiolabeled IL-13 or IL-13/onconase immunotoxin for therapy of colon, lung, breast, pancreatic, gastric, ovarian and medullary thyroid carcinoma.

REFERENCE COUNT: 8

REFERENCE(S):
(1) Akzo, N; WO 9200762 A 1992
(2) Genetics Inst; WO 9731946 A 1997
(3) Goldenberg, D; WO 9816254 A 1998
(6) Maclean, J; JOURNAL OF IMMUNOLOGY 1995, V155(7), P3674 CAPLUS
(7) Seipelt, I; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1997, V239(2), P534 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 17 OF 82 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:421800 CAPLUS

DOCUMENT NUMBER: 131:69273

TITLE: Recombinant Rhabdoviruses expressing the Paramyxovirus F protein in order to facilitate fusion and entry of the Rhabdovirus into a ***target*** cell

INVENTOR(S): Whitt, Michael A.; Robinson, Clinton S.

PATENT ASSIGNEE(S): University of Tennessee Research Corporation, USA

SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932648	A1	19990701	WO 1998-US26084	19981222

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,

CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9919056 A1 19990712 AU 1999-19056 19981222
PRIORITY APPLN. INFO.: US 1997-68472 19971222
WO 1998-US26084 19981222

AB This invention relates to a genetically engineered Rhabdovirus that expresses a ***fusion*** ***protein*** (preferably the F protein of the Paramyxovirus (PV) SV5 strain) which facilitates fusion and entry of the Rhabdovirus into a ***target*** cell. Provided is a recombinant Vesicular Stomatitis Virus (VSV) which expresses the F protein (PV) on the surface of the VSV particle. Also provided is a recombinant Rabies Virus (RV) encoding a F protein (PV)/G protein (RV) ***fusion*** ***protein*** . The provided recombinant Rhabdovirus may further express a second heterologous protein which may be used as an attachment protein or antireceptor to ***target*** the virus to a particular receptor present on the cell membrane of the ***target*** cell. Preferably, said attachment protein is the CD4 protein, and the virus is ***targeted*** to the GP120 protein on cells infected with HIV. The recombinant Rhabdoviruses of the invention can be used for purposes of research, as well as for diagnostic and ***therapeutic*** compns. for ***treatment*** of diseases.

REFERENCE COUNT: 5
REFERENCE(S):
(1) Lamb, R; Virology 1993, V197, P1 CAPLUS
(2) Mebatsion, T; Proceedings of the National Academy of Sciences of the USA 1996, V93, P11366 CAPLUS
(3) Schnell, M; Cell 1997, V90(5), P849 CAPLUS
(4) Schnell, M; Proceedings of the National Academy of Sciences of the USA 1996, V93, P11359 CAPLUS
(5) Stillman, E; Journal of Virology 1995, V69(5), P2946 CAPLUS

L33 ANSWER 18 OF 82 MEDLINE
ACCESSION NUMBER: 1999362679 MEDLINE
DOCUMENT NUMBER: 99362679
TITLE: A catalytic switch and the conversion of streptokinase to a fibrin- ***targeted*** plasminogen activator.
AUTHOR: Reed G L; Houng A K; Liu L; Parhami-Seren B; Matsueda L H; Wang S; Hedstrom L
CORPORATE SOURCE: Harvard School of Public Health, Harvard University, Boston, MA 02115, USA.. reed@cvlab.harvard.edu
CONTRACT NUMBER: HL-02348 (NHLBI)
HL-57314 (NHLBI)
AI-33175 (NIAID)
+
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Aug 3) 96 (16) 8879-83. Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199911
ENTRY WEEK: 19991103

AB Plasminogen (Pg) activators such as streptokinase (SK) save lives by generating plasmin to dissolve blood clots. Some believe that the unique ability of SK to activate Pg in the absence of fibrin limits its ***therapeutic*** utility. We have found that SK contains an unusual

NH(2)-terminal "catalytic switch" that allows Pg activation through both fibrin-independent and fibrin-dependent mechanisms. Unlike SK, a mutant (rSKDelta59) ***fusion*** ***protein*** lacking the 59 NH(2)-terminal residues was no longer capable of fibrin-independent Pg activation (k(cat)/K(m) decreased by >600-fold). This activity was restored by coincubation with equimolar amounts of the NH(2)-terminal peptide rSK1-59. Deletion of the NH(2) terminus made rSKDelta59 a Pg activator that requires fibrin, but not fibrinogen, for efficient catalytic function. The fibrin-dependence of the rSKDelta59 activator complex apparently resulted from selective catalytic processing of fibrin-bound Pg substrates in preference to other Pg forms. Consistent with these observations, the presence (rSK) or absence (rSKDelta59) of the
SK NH(2)-terminal peptide markedly altered fibrinolysis of human clots suspended in plasma. Like native SK, rSK produced incomplete ***clot*** lysis and complete destruction of plasma fibrinogen; in contrast, rSKDelta59 produced total ***clot*** lysis and minimal fibrinogen degradation. These studies indicate that structural elements in the NH(2) terminus are responsible for SK's unique mechanism of fibrin-independent Pg activation. Because deletion of the NH(2) terminus alters SK's mechanism of action and ***targets*** Pg activation to fibrin, there is the potential to improve SK's ***therapeutic*** efficacy.

L33 ANSWER 19 OF 82 MEDLINE
ACCESSION NUMBER: 1999441364 MEDLINE
DOCUMENT NUMBER: 99441364
TITLE: An antibody-avidin ***fusion*** ***protein*** specific for the transferrin receptor serves as a delivery vehicle for effective brain ***targeting*** : initial applications in anti-HIV antisense drug delivery to the brain.
AUTHOR: Penichet M L; Kang Y S; Pardridge W M; Morrison S L; Shin S
U
CORPORATE SOURCE: Department of Microbiology, The Molecular Biology Institute, University of California, Los Angeles 90095, USA.
CONTRACT NUMBER: CA-16042 (NCI)
AI-29470 (NIAID)
RO1-NS-34698 (NINDS)
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Oct 15) 163 (8) 4421-6.
Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 200001
ENTRY WEEK: 20000104
AB In the present study a novel Ab-avidin ***fusion*** ***protein*** has been constructed to deliver biotinylated compounds across the blood brain barrier. This fusion molecule consists of an Ab specific for the transferrin receptor genetically fused to avidin. The Ab-avidin ***fusion*** ***protein*** (anti-TfR IgG3-CH3-Av) expressed in murine myeloma cells was correctly assembled and secreted and showed both Ab- and avidin-related activities. In animal models, it showed much longer
serum half-life than the chemical conjugate between OX-26 and avidin. Most
importantly, this ***fusion*** ***protein*** demonstrated

superior
[3H]biotin uptake into brain parenchyma in comparison with the chemical conjugate. We also delivered a biotinylated 18-mer antisense peptide-nucleic acid specific for the rev gene of HIV-1 to the brain. Brain uptake of the HIV antisense drug was increased at least 15-fold when it was bound to the anti-TfR IgG3-CH3-Av, suggesting its potential use in neurologic AIDS. This novel Ab ***fusion*** ***protein*** should have general utility as a universal vehicle to effectively deliver biotinylated compounds across the blood-brain barrier for diagnosis and/or ***therapy*** of a broad range of CNS disorders such as ***infectious*** diseases, brain tumors as well as Parkinson's and Huntington's diseases.

L33 ANSWER 20 OF 82 MEDLINE
ACCESSION NUMBER: 1999310527 MEDLINE
DOCUMENT NUMBER: 99310527
TITLE: ***Carcinoembryonic*** antigen (***CEA***)-specific T-cell activation in colon carcinoma induced by anti-CD3 x anti- ***CEA*** bispecific diabodies and B7 x anti- ***CEA*** bispecific fusion proteins.
AUTHOR: Holliger P; Manzke O; Span M; Hawkins R; Fleischmann B; Qinghua L; Wolf J; Diehl V; Cochet O; Winter G; Bohlen H
CORPORATE SOURCE: MRC Centre for Protein Engineering, Cambridge, United Kingdom.
SOURCE: CANCER RESEARCH, (1999 Jun 15) 59 (12) 2909-16.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990904
AB Two bispecific recombinant molecules, an anti-CD3 x anti-carcinoembryogenic antigen (***CEA***) diabody and a B7 x anti- ***CEA*** ***fusion*** ***protein*** , were tested for their capacity to specifically activate T cells in the presence of ***CEA*** -expressing colon carcinoma cells. T-cell activation by the anti-CD3 x anti- ***CEA*** diabody required close contact to ***CEA*** -positive cells and resulted in diabody-mediated cytotoxicity against the ***target*** cells. Additionally, CD28-mediated costimulation in combination with anti-CD3 x anti- ***CEA*** diabodies induced activation of autologous T cells in ***CEA*** -positive primary colon carcinoma specimens, as determined by flow cytometry. The high specificity of the bispecific diabody approach could be further enhanced by the use of B7 x anti- ***CEA*** fusion proteins because the costimulatory CD28-signaling to the T cells strictly depended on the expression of ***CEA*** on the ***target*** cells. We demonstrate that displaying engagement sites for the T-cell antigens CD3 and CD28 on the surface of colon carcinoma cells is a suitable way to activate and retarget T cells in a highly tumor-specific manner. For clinical purposes, B7 x anti-tumor-associated antigen (TAA) fusion proteins, which are equally effective but more specific compared with anti-CD28 monoclonal anti-bodies, thus may improve the tumor specificity of anti-CD3 x anti-TAA

bispecific antibodies. Furthermore, B7-negative tumors can be converted into B7-positive tumors by B7 x anti-TAA fusion proteins without the need for B7 gene transfer to the malignant cells.

L33 ANSWER 21 OF 82 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:310833 BIOSIS
DOCUMENT NUMBER: PREV199900310833
TITLE: Identification of a novel major histocompatibility complex class II-restricted tumor antigen resulting from a chromosomal rearrangement recognized by CD4+ T cells.
AUTHOR(S): Wang, Rong-Fu (1); Wang, Xiang; Rosenberg, Steven A.
CORPORATE SOURCE: (1) National Cancer Institute, NIH, Bldg. 10/Rm. 2B08, Bethesda, MD, 20892 USA
SOURCE: Journal of Experimental Medicine, (May 17, 1999) Vol. 189, No. 10, pp. 1659-1667.
ISSN: 0022-1007.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB CD4+ T cells play an important role in antitumor immune responses and autoimmune and ***infectious*** diseases. Although many major histocompatibility complex (MHC) class I-restricted tumor antigens have been identified in the last few years, little is known about MHC class II-restricted human tumor antigens recognized by CD4+ T cells. Here, we describe the identification of a novel melanoma antigen recognized by an human histocompatibility leukocyte antigen (HLA)-DR1-restricted CD4+ tumor-infiltrating lymphocyte (TIL) 1363 using a genetic cloning approach.
DNA sequencing analysis indicated that this was a fusion gene generated by
a low density lipid receptor (LDLR) gene in the 5' end fused to a GDP-L-fucose:beta-D-galactoside 2-alpha-L-fucosyltransferase (FUT) in an antisense orientation in the 3' end. The fusion gene encoded the first five ligand binding repeats of LDLR in the NH2 terminus followed by a new polypeptide translated in frame with LDLR from the FUT gene in an antisense direction. Southern blot analysis showed that chromosomal DNA rearrangements occurred in the 1363mel cell line. Northern blot analysis detected two fusion RNA transcripts present only in the autologous 1363mel, but not in other cell lines or normal tissues tested. Two minimal
peptides were identified from the COOH terminus of the ***fusion*** ***protein*** . This represents the first demonstration that a ***fusion*** ***protein*** resulting from a chromosomal rearrangement in tumor cells serves as an immune ***target*** recognized by CD4+ T cells.

L33 ANSWER 22 OF 82 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:184847 BIOSIS
DOCUMENT NUMBER: PREV199900184847
TITLE: Tumor ***targeting*** and therapy with an anticarcinoembryonic antigen (***CEA***) antibody-IL-2 ***fusion*** ***protein*** in transgenic mice.
AUTHOR(S): Xu, X.; Clarke, P.; Szalai, G.; Primus, F. J.
CORPORATE SOURCE: Beckman Res. Inst. City Hope, Duarte, CA 91010 USA
SOURCE: FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A645.
Meeting Info.: Annual Meeting of the Professional Research Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21, 1999
ISSN: 0892-6638.

DOCUMENT TYPE: Conference
LANGUAGE: English

L33 ANSWER 23 OF 82 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999359493 EMBASE
TITLE: Radiation absorbed dose estimation for 90Y-DOTA-biotin with
pretargeted NR-LU-10/streptavidin.
AUTHOR: Breitz H.B.; Fisher D.R.; Goris M.L.; Knox S.; Ratliff B.; Murtha A.D.; Weiden P.L.
CORPORATE SOURCE: Dr. H.B. Breitz, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98111, United States. hbbreitz@aol.com
SOURCE: Cancer Biotherapy and Radiopharmaceuticals, (1999) 14/5 (381-395).
Refs: 33
ISSN: 1084-9785 CODEN: CBRAFJ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Pretargeted radioimmunotherapy permits the administration of doses of 90Y five times higher than is possible with antibodies directly labeled with 90Yttrium (90Y). These high doses of90 Y introduced new issues for dosimetry that were not encountered in prior studies using conventional radioimmunotherapy. We have addressed these issues here and correlated dosimetry estimates with observed toxicity and tumor responses. Methods: The pretargeted radioimmunotherapy (PRIT(TM)) system employed the antibody NR-LU- 10 conjugated with streptavidin, a glycoprotein ***clearing*** ***agent*** and 90Y- DOTA-biotin. A single dose of 90Y was escalated to 140 mCi/m2. Indium -111 (111In) (3-5 mCi) DOTA-biotin was co-injected for gamma camera imaging and dosimetry assessment. The effect of bremsstrahlung radiation from increasing 90Y activity levels with a constant dose of rain was studied using a phantom. Patient images identified the intestinal tract and the kidneys as potential organs at risk of clinically significant radiation toxicity. A method of measuring the activity localized in the intestinal tract was developed, and S values were calculated to estimate intestinal wall dose from radioactivity present in the intestine. Intestinal, bone marrow and renal toxicity were observed. Coefficients were derived for correlating the relationships between observed intestinal and marrow toxicity and the estimated radiation absorbed doses. Results: At an 90Y: 111In ratio of 50: 1, bremsstrahlung radiation accounted for 12% of the counts in the images. Grade IV diarrhea was observed in patients estimated to have received 6850-14000 cGy to the large intestinal wall. The correlation coefficient of intestinal toxicity with absorbed dose was 0.64. Myelotoxicity (measured as grade of suppression of absolute neutrophil count) correlated better with marrow dose (r=0.72) than with the whole body dose, (r=0.44). Delayed renal toxicity was observed in two patients 8 and 11 months following ***therapy*** . Tumor response was seen in the two patients with the highest estimated dose to tumor, 4,000-6,000 cGy. Conclusion: Dosimetry is feasible using 111In as a tracer in the presence of high 90Y activity. The absorbed dose estimates derived in the PRIT schema correlated moderately well with clinically observed toxicity and

response.

L33 ANSWER 24 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:356245 CAPLUS
DOCUMENT NUMBER: 131:198375
TITLE: Functional identification of bispecific ***fusion*** ***protein*** of ***CEA*** single-chain antibody and streptavidin
AUTHOR(S): Ji, Wansheng; Ren, Jun; Zhou, Shaojuan; Fei, Jinxiu; Chen, Zheng; Qiao, Taidong; Fan, Daiming
CORPORATE SOURCE: Institute of Digestive Disease, Xijing Hospital, Fourth Military Medical University, Xi'an, 710033, Peop. Rep. China
SOURCE: Disi Junyi Daxue Xuebao (1999), 20(4), 297-299
CODEN: DJDXEG; ISSN: 1000-2790
PUBLISHER: Disi Junyi Daxue Xuebao Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB A ***fusion*** ***protein*** of ***carcinoembryonic*** antigen (***CEA***), single chain antibody fragment of variable region (ScFv), and streptavidin was expressed by pET21 prokaryotic expression system. The E. coli. strain HMS174 (DE3) was transformed by the fusion expression vector pACS, then induced to express ***target*** protein by 1 mmol L-1 IPTG. The ext. from the transformed strain was analyzed by protein affinity blot and immunol. dot assay. SDS-PAGE demonstrated that the apparent mol. wt. of the ***target*** protein was about 57 ku, and affinity blot and immunol. dot proved that the ***fusion*** ***protein*** had bispecific activity and could bind ***CEA*** and streptavidin resp. The bispecific ***fusion*** ***protein*** could be expressed by prokaryotic expression system and used to test ***CEA*** directly by biotinylated horseradish peroxidase (HRP).

L33 ANSWER 25 OF 82 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:441513 BIOSIS
DOCUMENT NUMBER: PREV199900441513
TITLE: Tumour ***targeting*** using MFE-23::TNFalpha ***fusion*** ***protein*** .
AUTHOR(S): Cooke, S. P. (1); Pedley, R. B. (1); Boden, R. (1); Holliger, P.; Winter, G.; Begent, R. H. J. (1); Chester, K. A. (1)
CORPORATE SOURCE: (1) CRC Targeting and Imaging Group, Dept. of Oncology, RFUCMS, UCL, Royal Free Campus, London, NW3 2PF UK
SOURCE: British Journal of Cancer, (July, 1999) Vol. 80, No. SUPPL. 2, pp. 85.
Meeting Info.: Joint Meeting of the British Association for Cancer Research, the British Oncological Association, the Association of Cancer Physicians and the Royal College of Radiologists Edinburgh, Scotland, UK July 11-14, 1999
ISSN: 0007-0920.
DOCUMENT TYPE: Conference
LANGUAGE: English

L33 ANSWER 26 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:8110 CAPLUS
DOCUMENT NUMBER: 130:62690
TITLE: Protein modules derived from tetranectins that can be used in the formation of trimeric proteins
INVENTOR(S): Thogersen, Hans Christian; Etzerodt, Michael; Holtet, Thor Las; Graversen, Niels Jonas Heilskov; Kastrup, Jette Sandholm; Nielsen, Bettina Bryde; Larsen, Ingrid Kjoller
PATENT ASSIGNEE(S): Den.
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9856906	A1	19981217	WO 1998-DK245	19980611
W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9879065	A1	19981230	AU 1998-79065	19980611
EP 1012280	A1	20000628	EP 1998-929225	19980611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			DK 1997-685	19970611
			WO 1998-DK245	19980611

AB Peptides derived from the trimerization domains of tetranectins (tetranectin trimerizing structural element (TTSE)) are described for use in the rational design of new multifunctional proteins that are new homo- or hetero- trimers. These proteins can be used in protein library technol., such as phage display technol., diagnostic and therapeutic systems, such as human gene therapy and imaging. The peptides are derived from the exon 3 sequence thought to have been involved in carbohydrate recognition. Oligomers of a ***fusion*** ***protein*** of cII repressor and TTSE and of TTSE were prepd. by expression of the genes in Escherichia coli. The proteins were recovered from inclusion bodies by solubilization and renaturation. Preformed oligomers were stable and did not subunit exchange in mixts. at room temps. After dissocn. by heating, mixed oligomers were formed.

REFERENCE COUNT: 8
REFERENCE(S):
(1) Berglund, L; Febs Letters 1992, V309(1), P15 CAPLUS
(2) Denzyme Aps; WO 9418227 A 1994
(3) Holtet, T; Protein Science 1997, V6(7), P1511 CAPLUS
(4) Kastrup, J; Febs Letters 1997, V412(2), P388
(7) Osbourn, J; Immunotechnology 1996, V2(3), P181 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 27 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:761969 CAPLUS
DOCUMENT NUMBER: 130:29189
TITLE: Fusion proteins of ***prodrug*** activating enzymes and ***targetting*** moieties and their therapeutic uses
INVENTOR(S): Emery, Stephen Charles; Blakey, David Charles
PATENT ASSIGNEE(S): Zeneca Limited, UK
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9851787	A2	19981119	WO 1998-GB1294	19980505
WO 9851787	A3	19990401		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9872254	A1	19981208	AU 1998-72254	19980505
GB 2338484	A1	19991222	GB 1999-22815	19980505
EP 979292	A2	20000216	EP 1998-919380	19980505
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
ZA 9803931	A	19981110	ZA 1998-3931	19980508
NO 995475	A	20000107	NO 1999-5475	19991109
PRIORITY APPLN. INFO.:			GB 1997-9421	19970510
			WO 1998-GB1294	19980505

AB A method of limiting ***prodrug*** activation to a specific cell type by ***targetting*** ***prodrug*** activating enzymes to that cell type as fusion proteins with cell-specific ligands is described. The cell-specific ligand may be an antibody, e.g. to a disease marker. Alternatively, the gene for the protein may be placed under control of a promoter that is only functional in the disease, e.g. a tumor marker gene.
Chimeric genes for fusion proteins of carboxypeptidase G2 (***CPG2***) and heavy and light chains of antibodies to ***carcinoembryonic*** antigen were constructed by std. methods. The ***fusion*** ***protein*** manufd. in animal cells dimerized through the dimerization domain of ***CPG2*** . The ***fusion*** ***protein*** was able to activate the ***prodrug*** PGP to the cytotoxic 4-[N,N-Bis(2-chloroethyl)amino]phenol. HCT116 cells transformed with the gene for this protein had an IC50 for PGP of 200 .mu.M compared to 1 .mu.M for the activated drug.

L33 ANSWER 28 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:728567 CAPLUS

DOCUMENT NUMBER: 130:10614
TITLE: Ricin precursors cleavable by disease-specific proteinases for ***treatment*** of cancer, viral or ***parasitic*** infections
INVENTOR(S): Borgford, Thor
PATENT ASSIGNEE(S): De Novo Enzyme Corp., Can.
SOURCE: PCT Int. Appl., 352 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9849311	A2	19981105	WO 1998-CA394	19980430
WO 9849311	A3	19990211		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9870237	A1	19981124	AU 1998-70237	19980430
EP 977862	A2	20000209	EP 1998-916743	19980430
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1997-45148	19970430
			US 1997-63715	19971029
			WO 1998-CA394	19980430

AB Ricin precursors with the ricin A and B chains linked by a protease-labile linker peptide are described for use in the ***treatment*** of disease. The linker peptide contains a cleavage site for a disease specific protease such as a cancer, fungal, viral or ***parasitic*** protease. The ricin A chain may be replaced by comparable cytotoxic proteins such as the abrin A chain. The protein is delivered to the ***target*** tissue using viral vectors carrying an expression cassette for the ricin ***fusion*** ***protein*** gene. Construction of a series of variants of preproricin cleavable by a no. of different proteinases is described. Cleavage and activation of these variants with the expected patterns of cleavage of rRNA is demonstrated.

L33 ANSWER 29 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:749352 CAPLUS
DOCUMENT NUMBER: 130:24108
TITLE: Therapeutic compounds comprised of anti-Fc receptor antibodies
INVENTOR(S): Deo, Yashwant M.; Goldstein, Joel; Graziano, Robert; Somasundaram, Chezian
PATENT ASSIGNEE(S): Medarex Inc, USA
SOURCE: U.S., 57 pp., Cont.-in-part of U. S. Ser. No. 484,172.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5837243	A	19981117	US 1996-661052	19960607
CA 2220461	AA	19961219	CA 1996-2220461	19960607
CN 1203603	A	19981230	CN 1996-196166	19960607

PRIORITY APPLN. INFO.: US 1995-484172 19950607

AB Multispecific multivalent mols. which are specific to an Fc receptor (FcR, Fc.gamma. receptor or Fc.gamma. RI) and to EGF, bombesin or ***carcinoembryonic*** antigen are described. These multivalent antibodies or humanized antibodies are useful inducing antibody-dependent cellular cytotoxicity against tumor cells such as breast cancer, sarcoma, carcinoma and ovarian cancer. Bispecific antibody comprising anti-Fc.gamma.RI (H22) and anti-HER2/neu antibodies was produced. H22-EGF ***fusion*** ***protein*** , H22-bombesin ***fusion*** ***protein*** , H22-heregulin ***fusion*** ***protein*** , and single chain bispecific anti-Fc.gamma.RI-anti- ***CEA*** mols. were prepd. for inducing antitumor cytotoxic T cells.

REFERENCE COUNT: 12

REFERENCE(S):
(1) Anon; WO 9105871 1991 CAPLUS
(3) Anon; WO 9205793 1992 CAPLUS
(4) Anon; WO 9410332 1994 CAPLUS
(5) Anon; WO 9509917 1995 CAPLUS
(6) Chen, J; Clinical Cancer Research 1995, V1(4), P425 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 30 OF 82 MEDLINE

ACCESSION NUMBER: 1998285697 MEDLINE
DOCUMENT NUMBER: 98285697
TITLE: Virion- ***targeted*** viral inactivation of human immunodeficiency virus type 1 by using Vpr fusion proteins.
AUTHOR: Kobinger G P; Borsetti A; Nie Z; Mercier J; Daniel N; Gottlinger H G; Cohen A
CORPORATE SOURCE: Departement de Microbiologie et Immunologie, Universite de Montreal, Montreal, Quebec, Canada H3C 3J7.
SOURCE: JOURNAL OF VIROLOGY, (1998 Jul) 72 (7) 5441-8.
Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199809
ENTRY WEEK: 19980901

AB Inactivation of progeny virions with chimeric virion-associated proteins represents a novel ***therapeutic*** approach against human immunodeficiency virus (HIV) replication. The HIV type 1 (HIV-1) Vpr gene product, which is packaged into virions, is an attractive candidate for such a strategy. In this study, we developed Vpr-based fusion proteins that could be specifically ***targeted*** into mature HIV-1 virions to affect their structural organization and/or functional integrity. Two Vpr fusion proteins were constructed by fusing to the first 88 amino acids of HIV-1 Vpr the chloramphenicol acetyltransferase enzyme (VprCAT) or the last 18 C-terminal amino acids of the HIV-1 Vpu protein (VprIE). These Vpr

fusion proteins were initially designed to quantify their efficiency of incorporation into HIV-1 virions when produced in cis from the provirus. Subsequently, CD4+ Jurkat T-cell lines constitutively expressing the VprCAT or the VprIE ***fusion*** ***protein*** were generated with retroviral vectors. Expression of the VprCAT or the VprIE ***fusion*** ***protein*** in CD4+ Jurkat T cells did not interfere with cellular viability or growth but conferred substantial resistance to HIV replication. The resistance to HIV replication was more pronounced in Jurkat-VprIE cells than in Jurkat-VprCAT cells. Moreover, the antiviral effect mediated by VprIE was dependent on an intact p6(gag) domain, indicating that the impairment of HIV-1 replication required the specific incorporation of Vpr ***fusion*** ***protein*** into virions. Gene expression, assembly, or release was not affected upon expression of these Vpr fusion proteins. Indeed, the VprIE and VprCAT fusion proteins were shown to affect the infectivity of progeny virus, since HIV virions containing the VprCAT or the VprIE fusion proteins were, respectively, 2 to 3 times and 10 to 30 times less ***infectious*** than the wild-type virus. Overall, this study demonstrated the successful transfer of resistance to HIV replication in tissue cultures by use of Vpr-based antiviral genes.

L33 ANSWER 31 OF 82 MEDLINE
ACCESSION NUMBER: 1998404122 MEDLINE
DOCUMENT NUMBER: 98404122
TITLE: Prodrugs of anthracyclines for use in antibody-directed enzyme ***prodrug*** therapy.
AUTHOR: Florent J C; Dong X; Gaudel G; Mitaku S; Monneret C; Gesson J P; Jacquesy J C; Mondon M; Renoux B; Andrianomenjanahary S; Michel S; Koch M; Tillequin F; Gerken M; Czech J; Straub R; Bosslet K
CORPORATE SOURCE: UMR 176 CNRS/Institut Curie, Section Recherche, 26 rue d'Ulm, F-75248 Paris Cedex 05, France.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1998 Sep 10) 41 (19) 3572-81.
Journal code: J0F. ISSN: 0022-2623.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199812
ENTRY WEEK: 19981202
AB A series of new prodrugs of daunorubicin and doxorubicin which are candidates for antibody-directed enzyme ***prodrug*** therapy (***ADEPT***) is reported. These compounds (25a,b,c and 32a,b,c) have been designed to generate cytotoxic drugs after activation with beta-glucuronidase. As expected, recovery of the active drug was observed after enzymatic cleavage by Escherichia coli beta-glucuronidase as well as by a ***fusion*** ***protein*** which has been obtained from human beta-glucuronidase and humanized ***CEA*** -specific binding region. The six prodrugs are highly stable and are more than 100-fold less cytotoxic than doxorubicin against murine L1210 cell lines. The ortho-substituted phenyl carbamates 25a,b,c are better substrates for

beta-glucuronidase than the corresponding para-substituted analogues. After taking into account additional factors such as stability in plasma and kinetics of enzymatic cleavage, we selected the o-nitro ***prodrug*** 25c for clinical trials.

L33 ANSWER 32 OF 82 MEDLINE
ACCESSION NUMBER: 1998408022 MEDLINE
DOCUMENT NUMBER: 98408022
TITLE: Enhanced antitumour effect of liposomal daunorubicin using antibody-phospholipase C conjugates or ***fusion*** ***protein*** .
AUTHOR: Carter G; White P; Fernie M; King S; McLean G; Titball R; Carr F J
CORPORATE SOURCE: Biovation Limited, AURIS Business Centre, Aberdeen AB23 8XU, UK.
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (1998 Oct) 13 (4) 819-25.
Journal code: CX5. ISSN: 1019-6439.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
AB We have developed a new two-step method for ***targeting*** cytotoxic drugs to tumour cells. The method firstly involves the binding to tumour cells of antibody-phospholipase C immunoconjugates or fusion proteins. Further to washing or clearance of the immunoconjugates, liposomes are introduced which are specifically lysed at the tumour site by PLC to release their cytotoxic contents in the vicinity of the tumour cells. For two alternative human cell lines, a synergistic inhibition of cell proliferation was seen for combined treatment with a specific immunoconjugate and daunorubicin encapsulated liposomes. For tumour xenografts in mice, the combined treatment resulted in an inhibition of tumour growth although with no eradication of tumours at the doses used. The two-step antibody-PLC/liposome approach offers broad possibilities for the precise delivery of payloads of cytotoxic drugs to tumour sites.

L33 ANSWER 33 OF 82 MEDLINE
ACCESSION NUMBER: 1998419594 MEDLINE
DOCUMENT NUMBER: 98419594
TITLE: Recombinant adenoviral delivery for in vivo expression of scFv antibody fusion proteins.
AUTHOR: Whittington H A; Ashworth L J; Hawkins R E
CORPORATE SOURCE: University Department of Oncology, Bristol Oncology Centre, UK.
SOURCE: GENE THERAPY, (1998 Jun) 5 (6) 770-7.
Journal code: CCE. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY WEEK: 19981203
AB Antibodies and their recombinant fragments have enormous potential for therapy of malignant and other diseases, but there can be problems associated with their production and purification in the quantities required for therapeutic use. We investigated the use of gene therapy for the production of such recombinant antibody fragments in vivo. We

generated two recombinant adenoviruses expressing the single chain Fvs (scFvs) fused to murine GM-CSF (mGM-CSF). The scFvs used are MFE-23 which binds to a human tumour-associated marker carcino-embryonic antigen (***CEA***) and B1.8 which binds the hapten 4-hydroxy-3-nitro-5-iodo-phenylacetyl (NIP). Using scFvs to ***target*** GM-CSF to tumour cells should reduce the systemic toxicity of GM-CSF but retain its ability as a cytokine to induce systemic immune responses to tumour ***targets*** . Cell lines infected with the recombinant adenoviruses in vitro express and secrete high levels of the scFv.mGM-CSF fusion proteins. The scFv retains specificity while the mGM-CSF portion is fully bioactive and there is no detectable degradation of the fusion product. We also demonstrated effective in vivo expression of the scFv.mGM-CSF proteins. C57BI/6 mice injected intravenously with the adenovirus encoding the MFE-23.mGM-CSF fusion produce high levels of the ***fusion*** ***protein*** by 2 days after infection. The scFv.mGM-CSF protein can be detected in the serum, at biologically active levels, for at least 20 days and the level of protein produced is related to the amount of adenovirus injected. This approach has the potential to streamline the testing of the many therapeutic strategies based on recombinant scFvs and we are currently testing these constructs in an animal model for antitumour activity.

L33 ANSWER 34 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:746162 CAPLUS
DOCUMENT NUMBER: 128:33794
TITLE: Monoclonal antibody to ***CEA*** , conjugates comprising the antibody, and their therapeutic use in an ***ADEPT*** system
INVENTOR(S): Copley, Clive Graham; Edge, Michael Derek; Emery, Stephen Charles
PATENT ASSIGNEE(S): Zeneca Limited, UK; Copley, Clive Graham; Edge, Michael Derek; Emery, Stephen Charles
SOURCE: PCT Int. Appl., 207 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
0	WO 9742329	A1	19971113	WO 1997-GB1165	19970429
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2250579	AA	19971113	CA 1997-2250579	19970429
	AU 9726455	A1	19971126	AU 1997-26455	19970429
	AU 719513	B2	20000511		
	EP 896626	A1	19990217	EP 1997-918258	19970429
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1217750	A	19990526	CN 1997-194390	19970429
	BR 9708910	A	19990803	BR 1997-8910	19970429
	NO 9805120	A	19981229	NO 1998-5120	19981103

PRIORITY APPLN. INFO.: GB 1996-9405 19960504
GB 1997-3103 19970214
WO 1997-GB1165 19970429

AB Disclosed is a mouse anti- ***CEA*** (***carcinoembryonic*** antigen) monoclonal antibody 806.077 useful for the diagnosis and therapy of cancer. The antibody complementarity detg. regions (CDRs) have the following sequences: heavy chain CDR1 DNYMH, CDR2 WIDPENGDTEYAPKFRG, CDR3 LIYAGYLAMDY; and light chain CDR1 SASSSVTYMH, CDR2 STSNLAS, CDR3 QQRSTYPLT. The antibody is preferably in the form of a conjugate with either an enzyme suitable for use in an ***ADEPT*** (antibody directed enzyme ***prodrug*** therapy) system, esp. a carboxypeptidase, or with a co-stimulatory mol. such as the extracellular domain of human B7.1 (or CD80). Prepn. of 806.077 antibody F(ab')2-carboxypeptidase G2 conjugate, cloning of the cDNA encoding antibody 806.077, and prepn. of humanized antibodies were shown.

L33 ANSWER 35 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:679116 CAPLUS
DOCUMENT NUMBER: 127:330381
TITLE: Modified/chimeric superantigens and their use
INVENTOR(S): Antonsson, Per; Hansson, Johan; Bjork, Per; Dohlsten, Mikael; Kalland, Terje; Abrahmsen, Lars; Forsberg, Goran
PATENT ASSIGNEE(S): Pharmacia & Upjohn AB, Swed.; Antonsson, Per; Hansson, Johan; Bjork, Per; Dohlsten, Mikael; Kalland, Terje; Abrahmsen, Lars; Forsberg, Goran
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9736932	A1	19971009	WO 1997-SE537	19970326
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2222757	AA	19971009	CA 1997-2222757	19970326
AU 9725251	A1	19971022	AU 1997-25251	19970326
AU 707827	B2	19990722		
EP 835266	A1	19980415	EP 1997-916693	19970326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1194651	A	19980930	CN 1997-190630	19970326
BR 9702179	A	19990316	BR 1997-2179	19970326
NO 9705435	A	19980129	NO 1997-5435	19971126

PRIORITY APPLN. INFO.: SE 1996-1245 19960329
US 1996-695692 19960812
WO 1997-SE537 19970326

AB A conjugate between a ***target*** -seeking moiety and a modified

superantigen, characterized in that the superantigen is a wild-type superantigen (SA I) in which an amino acid residue in a superantigen region (region I) detg. binding to TCR, preferably TCR V.beta., and T cell activation have been replaced by another amino acid residue while retaining the ability to activate a subset of T cells. In a preferred embodiment the modified superantigen is a chimer between at least two wild-type superantigens (SA I, SA II etc.) characterized in that one or more amino acid residues in a region detg. binding to TCR and T cell activation have been interchanged between various wild-type superantigens.

A ***therapeutic*** method making use of modified/chimeric superantigens as defined in the preceding paragraphs. An antibody prepn. in which the cysteine residues that provide for interchain disulfide bonds have been mutated so as to forbid interchain disulfide bridges, preferably to serine residues, for use as a pharmaceutical. Plasmid 5T4Fab-SEA encoding ***fusion*** ***protein*** contg. antibody 5T4 variable region and murine IgG1 V.kappa. chain and Staphylococcal enterotoxin A was constructed, and the expressed chimeric superantigen was tested.

L33 ANSWER 36 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:326866 CAPLUS
DOCUMENT NUMBER: 126:308798
TITLE: Chimeric DNA-binding/DNA methyltransferase nucleic acid and polypeptide and their uses
INVENTOR(S): Bestor, Timothy H.
PATENT ASSIGNEE(S): Trustees of Columbia University in the City of New York, USA; Bestor, Timothy H.
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9711972	A1	19970403	WO 1996-US15576	19960927
W: AU, CA, JP, MX, US, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9673781	A1	19970417	AU 1996-73781	19960927
PRIORITY APPLN. INFO.:			US 1995-4445	19950928
			US 1996-594866	19960131
			WO 1996-US15576	19960927

AB The present invention provides a chimeric protein which comprises a mutated DNA methyltransferase portion and a DNA binding protein portion that binds sufficiently close to a promoter sequence of a ***target*** gene (which promoter sequence contains a methylation site) to specifically methylate the site and inhibit activity of the promoter and thus inhibit expression of the ***target*** gene. This invention also provides for a method for inhibiting the expression of a ***target*** gene which includes contacting a promoter of the ***target*** gene with the chimeric protein, so as to specifically methylate the promoter sequence of

the ***target*** gene thus inhibiting expression of the ***target*** gene.

L33 ANSWER 37 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:342720 CAPLUS
DOCUMENT NUMBER: 127:64507
TITLE: Two-step pretargeting methods using improved biotin-active agent conjugates
INVENTOR(S): Reno, John M.; Theodore, Louis J.; Gustavson, Linda M.
PATENT ASSIGNEE(S): Neorx Corporation, USA
SOURCE: U.S., 80 pp. Cont.-in-part of U.S. Ser. No. 995,381, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5630996	A	19970520	US 1993-122979	19930916
US 5283342	A	19940201	US 1992-895588	19920609
US 5911969	A	19990615	US 1994-329617	19941026
PRIORITY APPLN. INFO.:			US 1992-895588	19920609
			US 1992-995381	19921223
			US 1992-995383	19921223

OTHER SOURCE(S): MARPAT 127:64507
AB Methods, compds., compns. and kits that relate to pretargeted delivery of diagnostic and ***therapeutic*** agents are disclosed. In particular, methods for radio-metal labeling of biotin and for improved radiohalogenation of biotin, as well as related compds., are described. Also, clearing agents, anti-ligand- ***targeting*** moiety conjugates, ***target*** cell retention enhancing moieties and addnl. methods are discussed. The method comprises (1) administering a 1st conjugate of antibody or fragment and streptavidin and allowing time for accumulation in ***target*** tissue (tumor), and (2) subsequently administering a 2nd biotindase-resistant conjugate of biotin and DOTA deriv. (chelated with radio-metal, e.g. 99mTc or 186Re). Asialoorosomucoid may be used as ***clearing*** ***agent*** for maximize ***targeting*** (tumor:blood) ratio.

L33 ANSWER 38 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:231479 CAPLUS
DOCUMENT NUMBER: 126:301783
TITLE: Hexose-derivatized human serum albumin clearing agents for use in pretargeting methods for diagnosis and ***therapy***
INVENTOR(S): Axworthy, Donald B.; Reno, John M.
PATENT ASSIGNEE(S): Neorx Corp., USA
SOURCE: U.S., 52 pp. Cont.-in-part of U.S. Ser. No. 995,383, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5616690	A	19970401	US 1993-133613	19931008
US 5283342	A	19940201	US 1992-895588	19920609
US 5914312	A	19990622	US 1994-297429	19940826
PRIORITY APPLN. INFO.:			US 1992-895588	19920609
			US 1992-995383	19921223

AB Clearing agents comprising hexose-derivatized human serum albumin and ligand mol.(s) are provided. These clearing agents are useful in pretargeting methods for e.g. cancer diagnosis or ***therapy*** to clear previously administered anti-ligand contg. conjugates. Preferably, the hexose is mannose or galactose and the ligand and anti-ligand are resp. biotin and avidin or streptavidin. Also described are related methodol. and compds., e.g. pretargeting protocols, radiometal labeling of biotin, radioiodination of biotin, and conjugates of anti-ligand (e.g streptavidin) and ***targeting*** moiety (e.g. monoclonal antibody).

L33 ANSWER 39 OF 82 MEDLINE

ACCESSION NUMBER:	97442348 MEDLINE
DOCUMENT NUMBER:	97442348
TITLE:	Construction of a novel virus that ***targets*** HIV-1-infected cells and controls HIV-1 infection [see comments].
COMMENT:	Comment in: Cell 1997 Sep 5;90(5):821-4
AUTHOR:	Schnell M J; Johnson J E; Buonocore L; Rose J K
CORPORATE SOURCE:	Department of Pathology, Yale University School of Medicine, New Haven, Connecticut 06510, USA.
CONTRACT NUMBER:	AI24345 (NIAID) AI49235 (NIAID)
SOURCE:	CELL, (1997 Sep 5) 90 (5) 849-57. Journal code: CQ4. ISSN: 0092-8674.
PUB. COUNTRY:	United States Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals; Cancer Journals
ENTRY MONTH:	199712

AB We describe a recombinant vesicular stomatitis virus lacking its glycoprotein gene and expressing instead the HIV-1 receptor CD4 and a coreceptor, CXCR4. This virus was unable to infect normal cells but did infect, propagate on, and kill cells that were first infected with HIV-1 and therefore had the HIV membrane ***fusion*** ***protein*** on their surface. Killing of HIV-1-infected cells controlled HIV infection in a T cell line and reduced titers of ***infectious*** HIV-1 in the culture by as much as 10(4)-fold. Such a ***targeted*** virus could have ***therapeutic*** value in reducing HIV viral load. Our results also demonstrate a general strategy of ***targeting*** one virus to the envelope protein of another virus to control infection.

L33 ANSWER 40 OF 82 MEDLINE

ACCESSION NUMBER:	97176623 MEDLINE
DOCUMENT NUMBER:	97176623
TITLE:	A tissue plasminogen activator/P-selectin ***fusion*** ***protein*** is an effective thrombolytic agent.
AUTHOR:	Fujise K; Revelle B M; Stacy L; Madison E L; Yeh E T; Willerson J T; Beck P J
CORPORATE SOURCE:	Department of Internal Medicine, University of Texas-Houston Health Science Center 77030, USA..

kfujise@heart.med.uth.tmc.edu
SOURCE: CIRCULATION, (1997 Feb 4) 95 (3) 715-22.
Journal code: DAW. ISSN: 0009-7322.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199705

AB BACKGROUND: P-selectin is expressed on the surface of activated endothelial cells and platelets. We hypothesized that a tissue plasminogen activator (TPA)/P-selectin ***fusion*** ***protein*** would have not only thrombolytic activity but also might ***target*** TPA to the thrombi. In addition, it seemed possible that this chimeric protein would competitively inhibit the binding of native P-selectin on endothelial cells and platelets to leukocytes and thus further promote thrombolysis. METHODS AND RESULTS: The full-length, plasminogen activator inhibitor-1-resistant form of TPA (TPAIR) together with two TPAIR/P-selectin fusion constructs (P280IR and P121IR) were expressed with the use of baculovirus vectors. After infection of Sf21 cells with the recombinant baculovirus, recombinant TPAIR and P-selectin/TPAIR fusion proteins were purified with the use of metal ion chromatography. The intact protease activity of TPAIR and the ligand binding capability of P-selectin were confirmed through indirect chromogenic and cell binding assays, respectively. These molecules were assessed both in vitro and in vivo for thrombolytic activity. In vitro ***clot*** lysis assays indicated equal efficacy of TPAIR, P280IR, and P121IR ($P > .5$). The in vivo efficacy was tested in a cyclic flow variation model with the use of the rat mesenteric artery. Compared with saline control ***treatment*** , reduction in cyclic flow variations was significant ($P < .05$) and similar ($P > .5$) among TPAIR, P280IR, and P121IR. No significant bleeding was noted among ***treated*** animals. CONCLUSIONS: Chimeric proteins P280IR and P121IR have ***clot*** lysis activities that are similar to TPAIR both in vitro and in vivo. These chimeric proteins also bind to P-selectin ligand in vitro. Thus, these proteins may provide an efficient method of ***targeting*** TPA to the thrombotic region. Further experimental analysis with the use of larger animal coronary occlusion models should help determine the future value of these proteins as clinical ***therapeutic*** agents.

L33 ANSWER 41 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:362455 CAPLUS
DOCUMENT NUMBER: 127:90197
TITLE: Single-chain Fv antibodies for ***targeting*** cancer therapy
AUTHOR(S): Begent, R. H. J.; Chester, K. A.
CORPORATE SOURCE: CRC Targeting and Imaging Group, Royal Free Hospital School of Medicine, London, NW3 2PF, UK
SOURCE: Biochem. Soc. Trans. (1997), 25(2), 715-717
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A ***fusion*** ***protein*** has been made incorporating the phage-derived single-chain Fv antibody to ***CEA*** (MFE-23) and ***CPG2*** with a hexahistidine tag for purifn. By using MFE-23, the antigen-binding moiety of the previously used antibody (A5B7) is replaced by one of 10-fold higher affinity. This ***fusion*** ***protein***

has been shown in preliminary animal tumor model expts. to give ratios of ***CPG2*** in tumor to blood of 70 after 72 h, compared with 7 for the conventional conjugate. Such fusion proteins may have useful advantages over conventional reagents for ***targeted*** cancer therapy.

L33 ANSWER 42 OF 82 MEDLINE

ACCESSION NUMBER: 97403091 MEDLINE
DOCUMENT NUMBER: 97403091
TITLE: Development of a streptavidin-anti-carcinoembryonic antigen antibody, radiolabeled biotin pretargeting method for radioimmunotherapy of colorectal cancer. Studies in a human colon cancer xenograft model.
AUTHOR: Sharkey R M; Karacay H; Griffiths G L; Behr T M; Blumenthal R D; Mattes M J; ***Hansen H J*** ; Goldenberg D M
CORPORATE SOURCE: Garden State Cancer Center, Belleville, New Jersey 07109, USA.
CONTRACT NUMBER: CA-37895 (NCI)
CA-39841 (NCI)
SOURCE: BIOCONJUGATE CHEMISTRY, (1997 Jul-Aug) 8 (4) 595-604.
Journal code: A1T. ISSN: 1043-1802.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712

AB Pretargeting methodologies can produce high tumor:blood ratios, but their role in cancer radioimmunotherapy (RAIT) is uncertain. A pretargeting method was developed using a streptavidin (StAv) conjugate of MN-14 IgG, an anti-carcinoembryonic antigen (CEA) murine monoclonal antibody (mab) as the primary ***targeting*** agent, an anti-idiotype antibody (WI2 IgG) as a ***clearing*** ***agent*** , and DTPA- or DOTA-conjugated biotin as the radiolabeled ***targeting*** agent. A variety of reagents and conditions were examined to optimize this method. At 3 h, 111In-DTPA-peptide-biotin tumor uptake was 3.9 +/- 0.8% per gram and tumor:blood ratios were > 11:1. By 24 h, this ratio was 178:1, but tumor accretion declined in accordance with the gradual loss of StAv-MN-14 from the tumor. Tissue retention was highest in the liver and kidneys, but their tumor:organ ratios were > 2:1. Dosimetry predicted that radiolabeled MN-14 alone would deliver higher tumor doses than this pretargeting method. Increasing the specific activity and using DOTA-biotin in place of DTPA increased tumor uptake nearly 2-fold, but analysis of StAv-MN-14's biotin-binding capacity indicated over 90% of the initial biotin-binding sites were blocked within 24 h. Animals fed a biotin-deficient diet had 2-fold higher 111In-DOTA-biotin uptake in the tumor, but higher uptake also was observed in all normal tissues. Although exceptionally ***adept*** at achieving high tumor:blood ratios rapidly, the tumor uptake of radiolabeled biotin with this pretargeting method is significantly ($p < 0.0001$) lower than that with a radiolabeled antibody. Endogenous biotin and enhanced liver and kidney uptake may limit the application of this method to RAIT, especially when evaluating the method in animals, but with strategies to overcome these limitations, this

pretargeting method could be an effective ***therapeutic*** alternative.

L33 ANSWER 43 OF 82 MEDLINE
ACCESSION NUMBER: 97138345 MEDLINE
DOCUMENT NUMBER: 97138345
TITLE: Tethering human immunodeficiency virus type 1 preintegration complexes to ***target*** DNA promotes integration at nearby sites.
AUTHOR: Bushman F D; Miller M D
CORPORATE SOURCE: Infectious Disease Laboratory, Salk Institute for Biological Studies, La Jolla, California 92037, USA.
CONTRACT NUMBER: AI37489-02 (NIAID)
SOURCE: JOURNAL OF VIROLOGY, (1997 Jan) 71 (1) 458-64. Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199704
ENTRY WEEK: 19970402
AB Integration of retroviral cDNA in vivo is normally not sequence specific with respect to the integration ***target*** DNA. We have been investigating methods for directing the integration of retroviral DNA to predetermined sites, with the dual goal of understanding potential mechanisms governing normal site selection and developing possible methods for gene ***therapy*** . To this end, we have fused retroviral integrase enzymes to sequence-specific DNA-binding domains and investigated ***target*** site selection by the resulting proteins. In a previous study, we purified and analyzed a ***fusion*** ***protein*** composed of human immunodeficiency virus integrase linked to the DNA-binding domain of lambda repressor. This fusion could direct selective integration in vitro into ***target*** DNA containing lambda repressor binding sites. Here we investigate the properties of a fusion integrase in the context of a human immunodeficiency virus provirus. We used a fusion of integrase to the DNA binding domain of the zinc finger protein zif268 (IN-zif). Initially we found that the fusion was highly detrimental to replication as measured by the multinuclear activation of a galactosidase indicator (MAGI) assay for infected centers. However, we found that viruses containing mixtures of wild-type integrase and IN-zif were ***infectious*** . We prepared preintegration complexes from cells infected with these viruses and found that such complexes directed increased integration near zif268 recognition sites.

L33 ANSWER 44 OF 82 MEDLINE
ACCESSION NUMBER: 97363176 MEDLINE
DOCUMENT NUMBER: 97363176
TITLE: Antibody-directed enzyme ***prodrug*** ***therapy*** : pharmacokinetics and plasma levels of ***prodrug*** and drug in a phase I clinical trial.
AUTHOR: Martin J; Stribbling S M; Poon G K; Begent R H; Napier M; Sharma S K; Springer C J
CORPORATE SOURCE: CRC Centre for Cancer Therapeutics, Institute of Cancer Research, CRC Laboratory, Sutton, Surrey, UK.

SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (1997) 40 (3) 189-201.
Journal code: C9S. ISSN: 0344-5704.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199710

AB Antibody-directed enzyme ***prodrug*** ***therapy*** (***ADEPT***) was administered to ten patients in a phase I clinical trial. The aim was to measure plasma levels of the ***prodrug*** 4-[(2-chloroethyl)(2-mesyloxyethyl) amino] benzoyl-L-glutamic acid (CMDA) and the bifunctional alkylating drug (CJS11) released from it by the action of tumour-localised carboxypeptidase G2 (CPG2) enzyme. New techniques were developed to extract the ***prodrug*** and drug from plasma by solid-phase absorption and elution and to measure CPG2 activity in plasma and tissue. All extracts were analysed by high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS). CPG2 activity was found in metastatic tumour biopsies but not in normal tissue, indicating that localisation had been successful. The ***clearing*** ***agent*** SB43-gal, given at 46.5 mg/m2, achieved the aim of clearing non-tumour-localised enzyme in the circulation, indicating that conversion of ***prodrug*** to drug could take place only at the site of localised conjugate. Plasma ***prodrug*** did not always remain above its required threshold of 3 microM for the " ***therapeutic*** window" of 120 min after dosing, but the presence of residual ***prodrug*** after the first administration of each day indicated that this could be achieved during the remaining four doses over the following 8 h. Despite considerable inter-patient ***prodrug*** plasma concentration variability, the elimination half-life of the ***prodrug*** was remarkably reproducible at 18 +/- 8 min. Rapid appearance of the drug in plasma indicated that successful conversion from the ***prodrug*** had taken place, but also undesirable leakback from the site of localisation into the bloodstream. However, drug plasma levels fell rapidly by at least 50% at between 10 and 60 min with a half-life of 36 +/- 14 min. Analysis of the plasma extracts by LC/MS indicated that this technique might be used to confirm qualitatively the presence of ***prodrug*** , drug and their metabolites.

L33 ANSWER 45 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:132790 CAPLUS
DOCUMENT NUMBER: 126:143315
TITLE: ***Therapeutic*** compounds comprised of anti-Fc receptor antibodies
INVENTOR(S): Deo, Yashwant M.; Goldstein, Joel; Graziano, Robert; Somasundaram, Chezian
PATENT ASSIGNEE(S): Medarex, Inc., USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640789	A1	19961219	WO 1996-US9988	19960607
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2220461	AA	19961219	CA 1996-2220461	19960607
AU 9663835	A1	19961230	AU 1996-63835	19960607
EP 832135	A1	19980401	EP 1996-923279	19960607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1203603	A	19981230	CN 1996-196166	19960607
JP 11501522	T2	19990209	JP 1996-502133	19960607
PRIORITY APPLN. INFO.:			US 1995-484172	19950607
			WO 1996-US9988	19960607

AB Disclosed are multispecific multivalent mols. comprising an anti-FcR portion, an anti- ***target*** portion, and optionally an anti-enhancement factor portion. The multispecific antibodies are useful for ***treating*** cancer or ***infectious*** diseases. In example, bispecific antibodies of FcR-anti-her2/neu, H22 hinge region-epidermal growth factor, H2-heregulin (or gp30), H22-bombesin, H22-tetanus toxin, and anti-Fc.gamma.RI-anti- ***carcinoembryonic*** antigen were prepd. The tumor cell killing activity, T cell proliferation stimulating activity, or antigen-presenting activity of the resp. chimeric antibodies were tested.

L33 ANSWER 46 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:121366 CAPLUS
DOCUMENT NUMBER: 126:130594
TITLE: Improved delivery of diagnostic and ***therapeutic*** agents to a ***target*** site
INVENTOR(S): Griffiths, Gary L.; ***Hansen, Hans J.*** ; Govindan, Serengulam
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640245	A1	19961219	WO 1996-US8696	19960607
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2223261	AA	19961219	CA 1996-2223261	19960607
AU 9660384	A1	19961230	AU 1996-60384	19960607
AU 699216	B2	19981126		
EP 837696	A1	19980429	EP 1996-918023	19960607

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI

JP 11507046 T2 19990622 JP 1996-501204 19960607
PRIORITY APPLN. INFO.: US 1995-486166 19950607
WO 1996-US8696 19960607

AB An in vivo method for delivering a diagnostic or ***therapeutic*** agent to a ***target*** site in a mammal, wherein a ***targeting*** species including a ***targeting*** moiety and a diagnostic or ***therapeutic*** agent or a binding site for a subsequently administered diagnostic or ***therapeutic*** agent conjugate, the ***targeting*** moiety having a primary binding site whereby it specifically binds to the ***target*** , is administered and allowed to accrete at the ***target*** site, is improved by injecting into the circulatory system of the mammal a ***clearing*** ***agent*** that binds to the primary binding site of the ***targeting*** species, whereby non-localized primary ***targeting*** species is cleared from circulation. The method is esp. useful in pretargeting methods because the ***clearing*** ***agent*** does not remove the primary ***targeting*** species or block secondary binding sites of the primary ***targeting*** species. Described are prepn. of streptavidin/anti-carcinoembryonic antigen antibody (IMMU-14) conjugate, prepn. of biotin-carborane-dextran conjugate, prepn. of yttrium-90-labeled p-[5-(biotinamido)pentyl(amino)thioureayl]-2-benzyl-diethylenetriaminepentaacetic acid (BPD), in vivo localization of Y-90-BPD to pretargeted streptavidin-IMMU-14, localization of biotin-carborane-dextran to pretargeted streptavidin-IgG, delivery of In-111 to tumor xenografts using the invented pretargeting protocol, etc.

L33 ANSWER 47 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:363602 CAPLUS
DOCUMENT NUMBER: 125:80523
TITLE: .alpha.1-antitrypsin variants carrying thrombin-specificity peptides from antithrombin III that are inactive against activated protein C
INVENTOR(S): Hopkins, Paul C. R.; Carrell, Robin; Crowther, Damian; Stone, Stuart
PATENT ASSIGNEE(S): Ppl Therapeutics (Scotland) Ltd., UK
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9610638	A1	19960411	WO 1995-GB2155	19950912
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9534794	A1	19960426	AU 1995-34794	19950912

PRIORITY APPLN. INFO.: GB 1994-19804 19940930
GB 1995-2138 19950203
WO 1995-GB2155 19950912

AB Serine protease inhibitors (serpins) derived from .alpha.1-antitrypsin that are substantially ineffective against activated protein C; do not require activation by heparin; and that inhibit thrombin are described for use as antithrombotics. Preferred serpins are variants of .alpha.1-antitrypsin carrying a thrombin-specific ***target*** sequence derived from antithrombin-III (AT-III). Such serpins have the specificity and irreversibility of action of AT-III, but do not have to be co-administered with heparin.

L33 ANSWER 48 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:359818 CAPLUS
DOCUMENT NUMBER: 125:29272
TITLE: Radioactive phosphorus labeling of therapeutical proteins for clinical uses
INVENTOR(S): Leung, Shui-on; Hansen, Hans J.; Griffiths, Gary L.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9608506	A1	19960321	WO 1995-US11405	19950918
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2200088	AA	19960321	CA 1995-2200088	19950918
AU 9535488	A1	19960329	AU 1995-35488	19950918
EP 783516	A1	19970716	EP 1995-932443	19950918
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10511263	T2	19981104	JP 1995-510254	19950918

PRIORITY APPLN. INFO.: US 1994-308103 19940916
WO 1995-US11405 19950918

AB A method for labeling therapeutical proteins, e.g., antibodies, with 32P or 33P comprises prepg. a ***fusion*** ***protein*** contg. the antibodies and a protein kinase substrate is disclosed. Labeling is then carried out using proteinase kinase. Recombinant prepn. of a ***fusion*** ***protein*** comprised of humanized anti-***carcinoembryonic*** antigen (***CEA***) monoclonal antibody MN14 and a Kemptide deriv., WRRASLG,; and phosphorylation of the ***fusion*** ***protein*** in the presence of a protein kinase were demonstrated. The labeled ***targeting*** proteins bind specifically to diseased cells or tissue, which are killed by the radiation from the 32P or 33P.

L33 ANSWER 49 OF 82 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1996:321303 CAPLUS
DOCUMENT NUMBER: 124:352674
TITLE: Use of the platelet-binding domain of the urokinase A-chain to bind drugs for ***treatment*** of cardiovascular diseases to platelets
INVENTOR(S): Gurewich, Victor
PATENT ASSIGNEE(S): New England Deaconess Hospital Corporation, USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604004	A1	19960215	WO 1995-US9848	19950803
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5759542	A	19980602	US 1994-286748	19940805
EP 771211	A1	19970507	EP 1995-929376	19950803
R: AT, CH, DE, ES, FR, GB, IT, NL, SE				

PRIORITY APPLN. INFO.: US 1994-286748 19940805
WO 1995-US9848 19950803

AB A fragment of the A-chain of urokinase responsible for binding of the enzyme to the platelet outer membrane is used to ***target*** drugs for ***treatment*** of cardiovascular disease. Conjugates of the drug and the urokinase are incorporated into the platelet outer membrane. The half-life of the conjugate in plasma is thereby increased to about 4 to 5 days, and it is automatically ***targeted*** to forming thrombi and sites of vascular injury. The fusion drug can thus be used to ***treat*** cardiovascular diseases, e.g., as adjunctive ***therapy*** to inhibit reocclusions in a patient after thrombolytic ***therapy*** or angioplasty. The drug may be manufd. as a ***fusion*** ***protein*** , e.g. with hirudin, or by chem. conjugation.

L33 ANSWER 50 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:200181 CAPLUS
DOCUMENT NUMBER: 124:229991
TITLE: A conjugate between a modified superantigen and a ***target*** -seeking compound and the use of the conjugate
INVENTOR(S): Abrahmsen, Lars; Bjoerk, Per; Dohlsten, Mikael; Kalland, Terje
PATENT ASSIGNEE(S): Pharmacia Ab, Swed.
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9601650	A1	19960125	WO 1995-SE681	19950607
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

SE 9402430	A	19960112	SE 1994-2430	19940711
CA 2194673	AA	19960125	CA 1995-2194673	19950607
AU 9529940	A1	19960209	AU 1995-29940	19950607
AU 699147	B2	19981126		
EP 766566	A1	19970409	EP 1995-926057	19950607

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

CN 1152877	A	19970625	CN 1995-194071	19950607
HU 77257	A2	19980302	HU 1997-63	19950607
JP 11500407	T2	19990112	JP 1995-504251	19950607
ZA 9505746	A	19960220	ZA 1995-5746	19950711
FI 9700100	A	19970110	FI 1997-100	19970110
NO 9700108	A	19970220	NO 1997-108	19970110
PRIORITY APPLN. INFO.:			SE 1994-2430	19940711
			WO 1995-SE681	19950607

AB A conjugate comprising (a) a biospecific affinity counterpart (***target*** -seeking group) that binds to a predetd. structure and (b) a peptide that (i) contains an amino acid sequence that is derived from a superantigen, and (ii) has the ability of binding to a V.beta. chain of a T-cell receptor, and (iii) has a modified ability to bind to a MHC class II antigen compared to the superantigen from which the peptide is derived, which parts are covalently linked together. The conjugate is a ***fusion*** ***protein*** ; the bispecific affinity counterpart is an antibody; and the superantigen is staphylococcal enterotoxin A, B, C1, C2, D, E or H. The conjugate is useful for activating T lymphocytes to lyse ***target*** cells and for ***treating*** cancer, viral infection, autoimmune disease, or ***parasite*** infestation. In example, recombinant ***fusion*** ***protein*** contg. monoclonal anti-GA-733 antibody fragment and staphylococcal enterotoxin A was prepd. and tested for it cytotoxicity against MHC class II+ Raji cells, MHC class II- colon carcinoma cells SW 620.

L33 ANSWER 51 OF 82 MEDLINE
ACCESSION NUMBER: 96256741 MEDLINE
DOCUMENT NUMBER: 96256741
TITLE: ***Therapeutic*** effect of Gag-nuclease ***fusion*** ***protein*** on retrovirus-infected cell cultures.
AUTHOR: Schumann G; Qin L; Rein A; Natsoulis G; Boeke J D
CORPORATE SOURCE: Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
SOURCE: JOURNAL OF VIROLOGY, (1996 Jul) 70 (7) 4329-37. Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199610

AB Capsid- ***targeted*** viral inactivation is a novel protein-based strategy for the ***treatment*** of viral infections. Virus particles are inactivated by ***targeting*** toxic fusion proteins to virions, where they destroy viral components from within. We have fused Staphylococcus nuclease (SN) to the C-terminal end of Moloney murine leukemia virus Gag and demonstrated that expression of this

fusion
protein in chronically infected chicken embryo fibroblasts resulted in its incorporation into virions and subsequent inactivation of the virus particles by degradation of viral RNA. Release of particles incorporating Gag-SN fusion proteins into the extracellular milieu activates the nuclease and results in destruction of the virion from within. By comparing the effects of incorporated SN and SN*, an enzymatically inactive missense mutant form of SN, on the infectivity of virus particles, we have clearly demonstrated that nucleolytic activity is the antiviral mechanism. Expression of Gag-SN fusion proteins as a ***therapeutic*** agent causes a stable reduction of ***infectious*** titers by 20- to 60-fold. The antiviral effect of capsid- ***targeted*** viral inactivation in our model system, using both prophylactic and ***therapeutic*** approaches, suggests that a similar anti-human immunodeficiency virus strategy might be successful.

L33 ANSWER 52 OF 82 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96256621 EMBASE
DOCUMENT NUMBER: 1996256621
TITLE: Mechanisms of mutations inhibiting fusion and infection by Semliki Forest virus.
AUTHOR: Kielian M.; Klimjack M.R.; Ghosh S.; Duffus W.A.
CORPORATE SOURCE: Department of Cell Biology, Albert Einstein College of Medicine,Bronx, NY 10461, United States
SOURCE: Journal of Cell Biology, (1996) 134/4 (863-872).
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Semliki Forest virus (SFV) infects cells by an acid-dependent membrane fusion reaction catalyzed by the virus spike protein, a complex containing E1 and E2 transmembrane subunits. E1 carries the putative virus fusion peptide, and mutations in this domain of the spike protein were previously shown to shift the pH threshold of cell-cell fusion (G91A), or block cell-cell fusion (G91D). We have used an SFV ***infectious*** clone to characterize virus particles containing these mutations. In keeping with the previous spike protein results, G91A virus showed limited secondary infection and an acid-shifted fusion threshold, while G91D virus was noninfectious and inactive in both cell-cell and virus-liposome fusion assays. During the low pH-induced SFV fusion reaction, the E1 subunit exposes new epitopes for monoclonal antibody (mAb) binding and forms an SDS-resistant homotrimer, the virus associates hydrophobically with the ***target*** membrane, and fusion of the virus and ***target*** membranes occurs. After low pH ***treatment*** , G91A spike proteins were shown to bind conformation-specific mAbs, associate with ***target*** liposome membranes, and form the E1 homotrimer. However, both G91A membrane association and homotrimer formation had an acid-shifted pH threshold and reduced efficiency compared to wt virus. In contrast, studies of the fusion-defective G91D mutant showed that the virus efficiently reacted with low pH as assayed by mAb binding and liposome association, but was essentially inactive in homotrimer formation. These results suggest that the G91D mutant is noninfectious

due
to a block in a late step in membrane fusion, separate from the initial reaction to low pH and interaction with the ***target*** membrane, and
involving the lack of efficient formation of the E1 homotrimer.

L33 ANSWER 53 OF 82 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:139061 BIOSIS
DOCUMENT NUMBER: PREV199799438264
TITLE: Clinical imaging with a single chain Fv anti- ***CEA*** ,
potential for application to antibody directed enzyme ***prodrug*** therapy.
AUTHOR(S): Begent, R. H. J.; Chester, K. A.; Napier, M. N.; Casey, J. L.; Green, M.; Hope-Stone, L. D.; Keep, P. A.; Johnson, C. J.; Hilson, A. J. W.; Robson, L.
CORPORATE SOURCE: CRC Targeting and Imaging Group, Royal Free Hosp. Sch. Med., London NW3 UK
SOURCE: Immunotechnology (Amsterdam), (1996) Vol. 2, No. 4, pp. 267.
Meeting Info.: 1996 Keystone Meeting on Exploring and Exploiting Antibody and Ig Superfamily Combining Sites Taos, New Mexico, USA February 22-28, 1996
ISSN: 1380-2933.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L33 ANSWER 54 OF 82 MEDLINE
ACCESSION NUMBER: 1998040658 MEDLINE
DOCUMENT NUMBER: 98040658
TITLE: In vitro and in vivo characterisation of a recombinant carboxypeptidase G2::anti- ***CEA*** scFv ***fusion***
protein .
AUTHOR: Michael N P; Chester K A; Melton R G; Robson L; Nicholas W;
Boden J A; Pedley R B; Begent R H; Sherwood R F; Minton N P
CORPORATE SOURCE: Department of Molecular Microbiology, Centre for Applied Microbiology and Research, Wiltshire, UK.
SOURCE: IMMUNOTECHNOLOGY, (1996 Feb) 2 (1) 47-57.
Journal code: CR0. ISSN: 1380-2933.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
AB BACKGROUND: There is considerable interest in the specific ***targeting*** of therapeutic agents to cancer cells. Of particular promise is a technique known as Antibody-Directed Enzyme ***Prodrug*** Therapy (***ADEPT***). In this approach an enzyme is ***targeted*** to the tumour by its conjugation to a tumour specific-antibody tumour. After allowing sufficient time for the conjugate to localise at the tumour
and clear from the circulatory system, a relatively non-toxic ***prodrug*** is administered. This ***prodrug*** is converted to a
highly cytotoxic drug by the action of the ***targeted*** enzyme localised at the tumour site. OBJECTIVES: To construct gene fusions between the pseudomonad carboxypeptidase G2 (***CPG2***) gene and DNA

encoding MFE-23 (an anti- ***carcinoembryonic*** antigen (***CEA***) single-chain Fv (scFv) molecule), derived from a phage display library. To overexpress the resultant gene fusions in Escherichia coli, and assess the in vitro and in vivo properties of the purified fusion proteins.

STUDY

DESIGN: To introduce unique cloning restriction sites into the 5'-end of the ***CPG2*** gene by site-directed mutagenesis to facilitate fusion to the 3'-end of the gene encoding MFE-23 (constructs with or without a flexible (Gly4Ser)3 linker-encoding sequence were designed). To overexpress the resultant gene fusions under transcriptional control of the lac promoter and to direct the fusion proteins produced to the periplasmic space of E. coli through translational coupling to the pelB signal peptide. RESULTS: Biologically active recombinant ***CPG2*** ::MFE-23 scFv fusion proteins were produced in E. coli and shown to possess enzyme and anti- ***CEA*** activity. Affinity chromatography followed by size exclusion gel filtration yielded approximately 0.7-1.4 mg/l from shake flask culture. The ***fusion*** ***protein*** in which the enzyme and antibody moieties were joined by a linker peptide was shown to be effectively localised in nude mice bearing human colon tumour xenografts, giving favourable tumour to blood ratios. CONCLUSION: MFE-23 scFv serves as an ideal candidate for the antibody arm of a bacterially expressed ***fusion*** ***protein*** with ***CPG2*** . The biological properties of this recombinant protein suggest that it may be employed for tumour specific ***prodrug*** activation. However, further assessment of its stability and pharmokinetics is required if genetic fusion is to be considered as an alternative to chemical conjugation.

L33 ANSWER 55 OF 82 MEDLINE

ACCESSION NUMBER: 97041560 MEDLINE

DOCUMENT NUMBER: 97041560

TITLE: ***Targeting*** gamma interferon to tumor cells by a genetically engineered ***fusion*** ***protein*** secreted from myeloma cells.

AUTHOR: Xiang J; Qi Y; Cook D; Moyana T

CORPORATE SOURCE: Saskatoon Cancer Center, Department of Microbiology, University of Saskatchewan, Canada.

SOURCE: HUMAN ANTIBODIES AND HYBRIDOMAS, (1996) 7 (1) 2-10. Journal code: A6A. ISSN: 0956-960X.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706

ENTRY WEEK: 19970601

AB The construction, synthesis and expression of a genetically engineered bifunctional antibody/cytokine ***fusion*** ***protein*** is described. To ***target*** IFN-tau to tumor cells, recombinant antibody techniques were used to construct a RM4/IFN-tau ***fusion*** ***protein*** containing the chimeric anti-tumor F(ab')2 (RM4) and the IFN-tau moiety. The recombinant cDNA of IFN-tau was linked to 3 prime end of the chimeric heavy-chain gene fragment (M4) containing the VH, the CH1 and the hinge region to form the fused heavy-chain gene fragment M4-IFN-tau. Transfection of the M4-IFN-tau gene fragment into a myeloma derived cell line VKCK which produced the chimeric light-chain of the same antibody, allowed the transfectant secreting the bifunctional ***fusion*** ***protein*** RM4/IFN-tau. The RM4/IFN-tau was

purified
by the affinity chromatography. Our data showed that the RM4/IFN-tau retained the TAG72 antigen-binding reactivity as well as the IFN-tau activity as measured in ELISA, FACS analysis of cell-surface TAG72 expression, immunohistochemical study, and up-regulation of cell-surface expression of ***CEA*** , HLA class I and class II antigens. Therefore, the bifunctional ***fusion*** ***protein*** RM4/IFN-tau may prove to be useful in ***targeting*** biological effects of the IFN-tau to tumor cells and in this way to stimulate the immune destruction of tumor cells.

L33 ANSWER 56 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:874731 CAPLUS
DOCUMENT NUMBER: 123:266107
TITLE: Pretargeting methods and compounds for pretargeted delivery of diagnostic and ***therapeutic*** agents
INVENTOR(S): Theodore, Louis J.; Meyer, Damon L.; Mallett, Robert W.; Kasina, Sudhakar; Reno, John M.; Axworthy, Donald B.; Gustavson, Linda M.
PATENT ASSIGNEE(S): Neorx Corp., USA
SOURCE: PCT Int. Appl., 250 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9515979	A1	19950615	WO 1994-US14174	19941207
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2178476	AA	19950615	CA 1994-2178476	19941207
EP 733066	A1	19960925	EP 1995-905334	19941207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
PRIORITY APPLN. INFO.:			US 1993-163188	19931207
			WO 1994-US14174	19941207

AB Methods, compds., compns. and kits that relate to pretargeted delivery of diagnostic and ***therapeutic*** agents are disclosed. Examples include e.g. in vivo anal. of a radiolabeled chelate-biotin conjugate administered after antibody pretargeting, ***clearing*** ***agent*** evaluation, two- and three-step pretargeting methodol., and prepn. of conjugates. The methodol. may also be used to increase photosensitizing agent localization.

L33 ANSWER 57 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:810646 CAPLUS
DOCUMENT NUMBER: 123:237820
TITLE: Pretargeting methods and compounds for pretargeted delivery of diagnostic and ***therapeutic*** agents
INVENTOR(S): Theodore, Louis J.; Axworthy, Donald B.; Reno, John M.
PATENT ASSIGNEE(S): Neorx Corp., USA
SOURCE: PCT Int. Appl., 239 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9515978	A1	19950615	WO 1994-US14172	19941207
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2178477	AA	19950615	CA 1994-2178477	19941207
EP 743956	A1	19961127	EP 1995-904859	19941207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1993-163184 19931207
WO 1994-US14172 19941207

AB Methods, compds., compns. and kits that relate to pretargeted delivery of diagnostic and ***therapeutic*** agents are disclosed. In particular, methods for radiometal labeling of biotin, as well as related compds., are described. Clearing agents and clearance mechanisms are also discussed. Examples include e.g. in vivo anal. of a radiolabeled chelate-biotin conjugate administered after antibody pretargeting, ***clearing*** ***agent*** evaluation, two- and three-step pretargeting methodol., and prepn. of conjugates.

L33 ANSWER 58 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:881452 CAPLUS
DOCUMENT NUMBER: 123:296614
TITLE: Pretargeting methods and compounds with reduced immunogenicity of ***targeting*** moiety-anti-ligand conjugates or other components employed in diagnostic and ***therapeutic*** pretargeting protocols
INVENTOR(S): Graves, Scott S.; Bjorn, Michael J.; Reno, John M.; Axworthy, Donald B.; Fritzberg, Alan R.; Theodore, Louis J.
PATENT ASSIGNEE(S): Neorx Corp., USA
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9515770	A1	19950615	WO 1994-US14223	19941209
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1993-164302 19931209
AB Methods, compds., compns., and kits that relate to pretargeted delivery of diagnostic and ***therapeutic*** agents are disclosed. In particular, methods and agents are provided for reducing the immunogenicity of ***targeting*** moiety-anti-ligand conjugates or other components employed in diagnostic and ***therapeutic*** pretargeting protocols.

Prepn. of various conjugates for use in the invention is included. Examples include e.g. in vivo anal. of a radiolabeled chelate-biotin conjugate administered after antibody pretargeting, ***clearing*** ***agent*** evaluation, two- and three-step pretargeting methodol., administration of a monoclonal antibody (MAb)-streptavidin conjugate in humans, and immunosuppression of MAb-contg. conjugates.

L33 ANSWER 59 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:795164 CAPLUS
DOCUMENT NUMBER: 123:225940
TITLE: Pretargeting methods and compounds comprising radiometal labeled biotin and biotin- or streptavidin-antibody conjugates
INVENTOR(S): Yau, Eric K.; Theodore, Louis J.; Gustavson, Linda M.
PATENT ASSIGNEE(S): Neorx Corp., USA
SOURCE: PCT Int. Appl., 180 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9515335	A2	19950608	WO 1994-US13485	19941122
WO 9515335	A3	19950720		
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6022966	A	20000208	US 1993-156565	19931122
EP 736035	A1	19961009	EP 1995-910066	19941122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09505831	T2	19970610	JP 1994-515670	19941122
PRIORITY APPLN. INFO.:			US 1993-156565	19931122
			US 1992-895588	19920609
			US 1992-995381	19921223
			WO 1993-US5406	19930607
			WO 1994-US13485	19941122

AB Methods, compds., compns. and kits that relate to pretargeted delivery of diagnostic and ***therapeutic*** agents are disclosed. In particular, methods for radiometal labeling of biotin, as well as related compds., are described. Articles of manuf. useful in pretargeting methods are also discussed. In example, 186Re-chelated biotin and biotinylated monoclonal antibody to human colon tumor (NR-LU-10) were prepd. and used in combination with avidin were performed in a 3-step pretargeting protocol in nude mice implanted with human colon tumor xenografts, and a enhanced tumor uptake of 186Re-chelated biotin in the presence of biotinylated antibody and avidin was obsd. Also, streptavidin-NR-LU-10 conjugates were prepd. and used in combination with 186Re-chelated biotin and asialoorosomucoid ***clearing*** ***agent*** (prepn. described) for two-step pretargeting protocol expt.

L33 ANSWER 60 OF 82 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95349890 EMBASE
DOCUMENT NUMBER: 1995349890
TITLE: A cysteine protease is a ***target*** for the enzyme structure-based design of antiparasitic drugs.

AUTHOR: Eakin A.E.; McKerrow J.H.; Craik C.S.
CORPORATE SOURCE: Department of Biochemistry, Puerto Rico Univ. School of Medicine, P.O. Box 365067,San Juan 00936-5067, Puerto Rico
SOURCE: Drug Information Journal, (1995) 29/SUPPL. (1501S-1517S). ISSN: 0092-8615 CODEN: DGIJB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Proteases have been shown to be factors in the pathogenicity of many ***parasitic*** diseases, either by inducing tissue damage and facilitating invasion or by enabling the ***parasites*** to salvage metabolites from host proteins. To study genes encoding cysteine proteases of ***parasites*** , a general method for cloning fragments of thiol protease genes was developed using the polymerase chain reaction (PCR) with degenerate oligonucleotide primers. Subsequently, a PCR-amplified gene fragment of the protozoan ***parasite*** , Trypanosoma cruzi, was used to isolate a full-length gene encoding a cysteine protease. At least six copies of the gene are organized in the genome as a tandem array. The high degree of sequence identity with the papain family of enzymes suggested the name 'cruzain.' A copy of the gene was expressed in bacteria as an inactive, insoluble fusion polypeptide. Subsequently, the ***fusion*** ***protein*** was solubilized in urea and refolded to produce a polyprotein which processed autocatalytically to yield active, recombinant enzyme. This expression method generated recombinant protease of sufficient quality and quantity for crystallization. Diffraction quality crystals of recombinant cruzain, inactivated with a peptide inhibitor shown to block growth of the ***parasites*** in infected human cells, have been produced and characterized. The studies presented herein will provide insight into the mechanism of action and structure of cruzain and may enable the development of specific inhibitors for antiparasitic chemotherapy in the ***treatment*** of Chagas' disease.

L33 ANSWER 61 OF 82 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95135798 EMBASE
DOCUMENT NUMBER: 1995135798
TITLE: Schistosoma mansoni: Molecular cloning and sequencing of the 200-kDa chemotherapeutic ***target*** antigen.
AUTHOR: Hall T.M.T.; Joseph G.T.; Strand M.
CORPORATE SOURCE: Pharmacol./Molecular Sciences Dept., Johns Hopkins Univ. Sch. of Medicine,Baltimore, MD 21205, United States
SOURCE: Experimental Parasitology, (1995) 80/2 (242-249). ISSN: 0014-4894 CODEN: EXPAAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Praziquantel is the drug of choice for human schistosomiasis. The efficacy of this drug is impaired in immune-deficient mice. However, transfer to B cell-depleted mice of a monoclonal antibody that recognizes a 200-kDa

GPI-
anchored glycoprotein of S. mansoni restores the effectiveness of praziquantel. In order to characterize this ***target*** antigen, we have isolated and sequenced cDNA clones encoding the 200-kDa protein. Three overlapping cDNA clones contained the complete nucleotide sequence. The sequences of five tryptic peptides from the native 200-kDa protein could be matched with regions in the amino acid sequence deduced from the nucleotide sequence of the isolated clones. This deduced amino acid sequence differed from sequences available in six databases. Praziquantel exposes epitopes on the worm surface that are normally not exposed, and we have shown by immunofluorescent staining that the ***fusion*** ***protein*** encoded by one of our cDNA clones expresses epitopes that are exposed on the surface of praziquantel- ***treated*** worms.

L33 ANSWER 62 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:558276 CAPLUS
DOCUMENT NUMBER: 123:25265
TITLE: ***Fusion*** ***protein*** -mediated tumor-selective ***prodrug*** activation
AUTHOR(S): Bosslet, Klaus; Czech, Joerg; Hoffmann, Dieter
CORPORATE SOURCE: Research Laboratories, Behringwerke AG, Marburg, Germany
SOURCE: Contrib. Oncol. (1995), 48, 160-9
CODEN: COONEV; ISSN: 0250-3220
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetics, tumor and tissue distribution and metab. of a ***fusion*** ***protein*** consisting of a humanized ***CEA*** -specific binding region and human .beta.-glucuronidase was studied. The kinetics of the ***fusion*** ***protein*** in normal organs parallels its concn. in plasma. It was shown that the ***fusion*** ***protein*** selectivity binds to ***CEA*** -pos. human tumor xenografts, remaining there as a functionally active mol. for at least 7 days. The pharmacokinetics of a doxorubicin ***prodrug*** N-[4-.beta.-glucuronyl-3-nitrobenzyloxycarbonyl]doxorubicin was detd. both with and without treatment with the ***fusion*** ***protein*** . Treatment with both ***fusion*** ***protein*** and ***prodrug*** resulted in an increased doxorubicin concn. in the ***target*** tissue (tumor transplant) and a decreased concn. in other tissues. Also, the combination of ***prodrug*** with ***fusion*** ***protein*** had antitumor activity, whereas ***prodrug*** alone or doxorubicin had no antitumor activity.

L33 ANSWER 63 OF 82 MEDLINE
ACCESSION NUMBER: 95156484 MEDLINE
DOCUMENT NUMBER: 95156484
TITLE: Crystal structures of a schistosomal drug and vaccine ***target*** : glutathione S-transferase from Schistosoma japonica and its complex with the leading antischistosomal drug praziquantel.
AUTHOR: McTigue M A; Williams D R; Tainer J A
CORPORATE SOURCE: Scripps Research Institute, Department of Molecular Biology-MB4, La Jolla, CA 92037.
CONTRACT NUMBER: AI08803 (NIAID)

SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1995 Feb 10) 246 (1) 21-7.
Journal code: J6V. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199505

AB Glutathione S-transferase (GST), an essential detoxification enzyme in ***parasitic*** helminths, is a major vaccine ***target*** and an attractive drug ***target*** against schistosomiasis and other helminthic diseases. Crystal structures of the 26 kDa GST from the helminth Schistosoma japonica (SjGST) have been determined for the unligated enzyme (resolution = 2.4 A, R-factor = 19.7%) and for the enzyme bound to the leading antischistosomal drug praziquantel (resolution = 2.6 A, R-factor = 21.2%). The protein, recombinantly expressed using the Pharamacia PGEX-3X vector for production of GST fusion proteins, contains all 218 residues of SjGST and an additional 13 residues at the C terminus.

The structure of unligated SjGST shows that the glutathione binding site pre-exists unchanged in the ligand-free enzyme and is conserved between ***parasitic*** and the mammalian class mu enzymes. At ***therapeutic*** concentrations the leading antischistosomal drug praziquantel (PZQ) binds one drug per enzyme homodimer in the dimer interface groove adjoining the two catalytic sites. This establishes a protein ***target*** for PZQ, identifies the GST non-substrate ligand transport site, and implicates PZQ in steric inhibition of SjGST catalytic and transport for large ligands. Thus, increased expression or mutagenesis of SjGST by the ***parasite*** may confer resistance to PZQ. Differences in the xenobiotic binding region between ***parasitic*** and mammalian GSTs reveal a distinct substrate repertoire for SjGST and, together with the newly identified PZQ binding site, provide the basis for design of novel antischistosomal drugs. Due to the widespread use expression systems based on SjGST fusions, the atomic structure of SjGST should also provide an important tool for phasing ***fusion*** ***protein*** structures by molecular replacement.

L33 ANSWER 64 OF 82 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95071170 EMBASE
DOCUMENT NUMBER: 1995071170
TITLE: Crystal structures of a schistosomal drug and vaccine ***target*** : Glutathione S-transferase from Schistosoma japonica and its complex with the leading antischistosomal drug praziquantel.
AUTHOR: McTigue M.A.; Williams D.R.; Tainer J.A.
CORPORATE SOURCE: The Scripps Research Institute, Department of Molecular Biology, 10666 North Torrey Pines Road,La Jolla, CA 92037, United States
SOURCE: Journal of Molecular Biology, (1995) 246/6 (21-27).
ISSN: 0022-2836 CODEN: JMOBAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Glutathione S-transferase (GST), an essential detoxification enzyme in ***parasitic*** helminths, is a major vaccine ***target*** and an attractive drug ***target*** against schistosomiasis and other helminthic diseases. Crystal structures of the 26 kDa GST from the helminth Schistosoma japonica (SjGST) have been determined for the unligated enzyme (resolution = 2.4 .ANG., R-factor = 19.7%) and for the enzyme bound to the leading antischistosomal drug praziquantel (resolution = 2.6 .ANG., X-factor = 21.2%). The protein, recombinantly expressed using the Pharamacia PGEX-3X vector for production of GST fusion proteins, contains all 218 residues of SjGST and an additional 13 residues at the C terminus. The structure of unligated SjGST shows that the glutathione binding site pre-exists unchanged in the ligand-free enzyme and is conserved between ***parasitic*** and the mammalian class .mu. enzymes. At ***therapeutic*** concentrations the leading antischistosomal drug praziquantel (PZQ) binds one drug per enzyme homodimer in the dimer interface groove adjoining the two catalytic sites. This establishes a protein ***target*** for PZQ, identifies the GST non-substrate ligand transport site, and implicates PZQ in steric inhibition of SjGST catalytic and transport for large ligands. Thus, increased expression or mutagenesis of SjGST by the ***parasite*** may confer resistance to PZQ. Differences in the xenobiotic binding region between ***parasitic*** and mammalian GSTs reveal a distinct substrate repertoire for SjGST and, together with the newly identified PZQ binding site, provide the basis for design of novel antischistosomal drugs. Due to the widespread use expression systems based on SjGST fusions, the atomic structure of SjGST should also provide an important tool for phasing ***fusion*** ***protein*** structures by molecular replacement.

L33 ANSWER 65 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:412729 CAPLUS
DOCUMENT NUMBER: 122:151369
TITLE: Modified glycosidation of fusion proteins of anti-tumor antibodies and ***prodrug*** activating enzymes and the use of the proteins in the ***targetted*** treatment of tumors
INVENTOR(S): Bosslet, Klaus; Czech, Joerg; Hoffmann, Dieter
PATENT ASSIGNEE(S): Behringwerke AG, Germany
SOURCE: Eur. Pat. Appl., 28 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 623352	A2	19941109	EP 1994-106394	19940425
EP 623352	A3	19950222		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
DE 4314556	A1	19941110	DE 1993-4314556	19930504
AU 9461829	A1	19941110	AU 1994-61829	19940502
AU 684750	B2	19980108		
CA 2122745	AA	19941105	CA 1994-2122745	19940503

JP 06319554 A2 19941122 JP 1994-117524 19940506
PRIORITY APPLN. INFO.: DE 1993-4314556 19930504
AB Bifunctional antibody-enzyme conjugates with a modified glycosidation patterns are described for use in the treatment of tumors. The antibody component of the conjugate specifically binds a tumor-specific antigen and the enzyme moiety activates a ***prodrug*** . The carbohydrate component includes at least one exposed carbohydrate residue selected from the group: mannose, galactose, N-acetylglucosamine, N-acetyllactose, glucose and fucose and the exposed group is generated by enzymic removal of terminal sialic acid or mannose groups with optional enzymic addn. of the new terminal sugar. Glycosidation contributes to increased relative concn. of the glycoproteins at the site of the tumor, and speeds clearance of the protein from the general circulation and non-tumor sites. The proteins are manufd. with a mammalian glycosidation pattern by expression of the cloned gene in a transgenic animal cell line or animal. Clearance studies carried out in CD-1 nude mice on glycosidated and non-glycosidated fusion proteins of a human .beta.-glucuronidase and a human antibody to a tumor antigen are presented.

L33 ANSWER 66 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:426877 CAPLUS
DOCUMENT NUMBER: 121:26877
TITLE: Activation of prodrugs by enzymes that are fusion products of catalytic domains and antigen-binding domains
INVENTOR(S): Gehrmann, Mathias; Seemann, Gerhard; Bosslet, Klaus; Czech, Joerg
PATENT ASSIGNEE(S): Behringwerke Aktiengesellschaft, Germany
SOURCE: Eur. Pat. Appl., 35 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 590530	A2	19940406	EP 1993-115418	19930924
EP 590530	A3	19970326		
EP 590530	B1	20000426		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
DE 4233152	A1	19940407	DE 1992-4233152	19921002
CA 2107513	AA	19940403	CA 1993-2107513	19931001
NO 9303520	A	19940405	NO 1993-3520	19931001
ZA 9307299	A	19940425	ZA 1993-7299	19931001
AU 9348791	A1	19940414	AU 1993-48791	19931004
AU 672431	B2	19961003		
JP 06228195	A2	19940816	JP 1993-271291	19931004

PRIORITY APPLN. INFO.: DE 1992-4233152 19921002
AB Activation of prodrugs of cytotoxins at a defined ***target*** site is achieved using a ***fusion*** ***protein*** of ***prodrug*** -activating enzyme and an antigen-binding domain specific for an antigen of the ***target*** site. A ***fusion*** ***protein*** of a humanized sFv fragment of an antibody to ***carcinoembryonic*** antigen and a human .beta.-glucuronidase was prepd. by expression of the

chimeric gene in BHK cells. The protein was shown to specifically bind ***CEA*** and to hydrolyze 4-methyl-umbelliferyl-.beta.-glucuronide. Manuf. of the ***fusion*** ***protein*** in yeast is demonstrated.
Pharmacokinetics of the ***fusion*** ***protein*** 0.8 .mu.g injected into tumor-bearing nude mice showed very rapid clearing of the protein from the plasma and all other organs. The highest levels of the protein were found in the tumor with a concn. of 6.2 ng/g tissue after 120
h compared to <0.1 ng/g for all other tissue tested.

L33 ANSWER 67 OF 82 MEDLINE
ACCESSION NUMBER: 94228536 MEDLINE
DOCUMENT NUMBER: 94228536
TITLE: Tumor-selective ***prodrug*** activation by ***fusion*** ***protein*** -mediated catalysis.
AUTHOR: Bosslet K; Czech J; Hoffmann D
CORPORATE SOURCE: Research Laboratories of Behringwerke AG, Marburg, Germany..
SOURCE: CANCER RESEARCH, (1994 Apr 15) 54 (8) 2151-9.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199408
AB A two component system, consisting of a ***fusion*** ***protein*** and an appropriate ***prodrug*** , suited to perform selective tumor therapy in vivo is presented. The ***fusion*** ***protein*** , due to its humanized ***carcinoembryonic*** antigen-specific variable region, specifically binds to ***carcinoembryonic*** antigen-expressing tumors and has an enzymatic activity comparable to that
of human beta-glucuronidase. The ***prodrug*** is a nontoxic glucuronide-spacer derivative of doxorubicin decomposing to doxorubicin by
enzymatic deglucuronidation. In vivo studies in nude mice bearing human ***carcinoembryonic*** antigen-expressing tumor xenografts revealed that
7 days after injection of 20 mg/kg ***fusion*** ***protein*** a high specificity ratio (> 100:1) was obtained between tumor and plasma or tumor and normal tissues. Injection of 250 mg/kg of ***prodrug*** at day 7 resulted in tumor therapeutic effects superior to those of conventional chemotherapy without any detectable toxicity. These superior therapeutic effects which were observed using established human tumor xenografts can be explained by the approximately 4-12-fold higher doxorubicin concentrations found in tumors of mice treated with ***fusion*** ***protein*** and ***prodrug*** than in those treated with the maximal tolerable dose of drug alone. The nondetectable toxicity in the animals treated with ***fusion*** ***protein*** and ***prodrug*** is probably caused by up to 5-fold lower drug concentrations in normal tissues compared to the animals treated with doxorubicin. Thus, a more tumor-selective therapy, resulting in stronger therapeutic effects and reduced toxicity seems to be possible by the appropriate use of the humanized nontoxic ***fusion*** ***protein*** and the nontoxic ***prodrug*** .

L33 ANSWER 68 OF 82 MEDLINE
ACCESSION NUMBER: 94168957 MEDLINE

DOCUMENT NUMBER: 94168957
TITLE: Clearance of circulating radio-antibodies using streptavidin or second antibodies in a xenograft model.
AUTHOR: Marshall D; Pedley R B; Boden J A; Boden R; Begent R H
CORPORATE SOURCE: Department of Clinical Oncology, Royal Free Hospital School of Medicine, London, UK.
SOURCE: BRITISH JOURNAL OF CANCER, (1994 Mar) 69 (3) 502-7. Journal code: AV4. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199406

AB The improved tumour to non-tumour ratios needed for effective tumour ***targeting*** with antibodies requires that blood background radioactivity is reduced. We investigated the effect of streptavidin as a ***clearing*** ***agent*** for 125I-labelled biotinylated anti-CEA antibodies in a human colon carcinoma xenograft model. By comparing the biodistribution of the monoclonal antibody A5B7 with four, nine or 22 biotins per antibody molecule, we investigated how the degree of biotinylation of the primary radiolabelled antibody affects its clearance with streptavidin. Limiting the degree of biotinylation limited blood clearance, whereas nine or 22 biotins per antibody molecule resulted in a 13- to 14-fold reduction in blood radioactivity, the streptavidin-biotinylated antibody complexes clearing rapidly via the liver and spleen.

Although a reduction in tumour activity was also seen, a 6.6-fold improvement in the tumour to blood ratio was achieved. A comparative study of streptavidin versus second antibody clearance was carried out using the polyclonal antibody PK4S biotinylated with 12 biotins per antibody molecule. This study indicated that second antibody was superior for clearance of the polyclonal antibody, resulting in a larger and faster reduction in blood radioactivity and improved tumour to blood ratios. In this case the primary antibody was polyclonal, and therefore non-uniformity of biotinylation may affect complexation with streptavidin.

Therefore, the degree of biotinylation and type of antibody must be carefully considered before the use of streptavidin clearance.

L33 ANSWER 69 OF 82 MEDLINE
ACCESSION NUMBER: 95254574 MEDLINE
DOCUMENT NUMBER: 95254574
TITLE: Analysis of antibody-enzyme conjugate clearance by investigation of ***prodrug*** and active drug in an ***ADEPT*** clinical study.
AUTHOR: Springer C J; Poon G K; Sharma S K; Bagshawe K D
CORPORATE SOURCE: Cancer Research Campaign Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey, UK.
SOURCE: CELL BIOPHYSICS, (1994) 24-25 193-207. Journal code: CQC. ISSN: 0163-4992.
PUB. COUNTRY: United States (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508

AB Antibody-directed enzyme ***prodrug*** ***therapy*** (***ADEPT***) separates the cytotoxic function from the ***targeting*** function (5). An antibody-carboxypeptidase G2 (CPG2) enzyme is delivered prior to the nontoxic ***prodrug*** , CMDA, which is converted to a cytotoxic drug by the action of the localized conjugate at the tumor site.

An indirect in vitro assay was developed to detect the presence of functional CPG2 in the plasma of patients in an ***ADEPT*** clinical trial. Compounds in the plasma of patients were characterized using liquid chromatography-mass spectrometry. Plasma at three different time points (prior to ***treatment*** , post-antibody-enzyme conjugate, and post-galactosylated anti-enzyme antibody ***clearing*** ***agent***) was added to the CMDA ***prodrug*** and analyzed. Conversion of the CMDA ***prodrug*** to its active drug indicates that CPG2-conjugate remains in the plasma. This technique will provide essential data for the timing of ***prodrug*** administration in ***ADEPT*** .

L33 ANSWER 70 OF 82 MEDLINE

ACCESSION NUMBER: 95096012 MEDLINE
DOCUMENT NUMBER: 95096012
TITLE: The transmembrane region of microsomal cytochrome P450 identified as the endoplasmic reticulum retention signal.
AUTHOR: Murakami K; Mihara K; Omura T
CORPORATE SOURCE: Department of Molecular Biology, Graduate School of Medical Science, Kyushu University, Fukuoka..
SOURCE: JOURNAL OF BIOCHEMISTRY, (1994 Jul) 116 (1) 164-75. Journal code: HIF. ISSN: 0021-924X.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503

AB Microsomal-type cytochrome P450s are integral membrane proteins bound to the membrane through their N-terminal transmembrane hydrophobic segment, the signal anchor sequence. To elucidate the determinants that enable the P450s to be located in the ER, we constructed cDNAs encoding chimeric proteins in which a secretory form of ***carboxyesterase*** , ***carboxyesterase*** Sec, was connected to the N-terminus of the full-length or truncated forms of a microsomal-type P450, P450(M1), and the constructed plasmids were expressed in COS cells. Since ***carboxyesterase*** Sec is an N-glycosylated secretory protein, endo H treatment could be used to determine whether these chimeric proteins were located in the ER or not. ***Carboxyesterase*** Sec with the N-terminal 20 amino acids, containing the transmembrane region, of P450(M1), was located in the ER, as determined from the endo H sensitivity of the expressed protein and immunofluorescence staining of the cells. As the expressed protein exhibited ***carboxyesterase*** activity, it was not retained in the ER through the BiP-dependent quality control system recognizing unfolded proteins. Another chimeric protein construct in which ***carboxyesterase*** Sec was connected to the C-terminal region of rat UDP-glucuronosyltransferase (UDP-GT), that contained a double-lysin ER retention motif, was also located in the ER, as determined from the endo

H
sensitivity and immunofluorescence staining. On the other hand, the sugar moiety of the ***carboxyesterase*** Sec connected to the transmembrane segment of UDP-GT, Sec/GTd, was partially resistant to the endo H treatment. From the results of immunofluorescent staining and cell fractionation, it was concluded that the Sec/GTd product was located in the Golgi apparatus. These observations indicated that the N-terminal hydrophobic segment of P450(M1) is sufficient for the ER membrane retention, whereas the transmembrane segment of UDP-GT is not. To determine whether microsomal P450s are recycled between the ER and Golgi compartments or not, a DNA construct encoding cathepsin D connected to the N-terminus of P450(M1) was prepared and expressed in COS cells. The ***fusion*** ***protein*** was phosphorylated, but the phosphorylation was sensitive to alkaline phosphatase. As a control, authentic cathepsin D was subjected to phosphorylation of its oligosaccharide chain that was resistant to the alkaline phosphatase treatment. Since GlcNAc-P-transferase, which forms the alkaline phosphatase-resistant phosphodiester in the sugar chains of lysosome-***targeting*** proteins, is located in the Golgi apparatus, it was concluded that the oligosaccharide chain of the cathepsin D portion of the ***fusion*** ***protein*** was not phosphorylated, and that the chimeric protein did not go to the Golgi apparatus.(ABSTRACT TRUNCATED AT 400 WORDS)

L33 ANSWER 71 OF 82 MEDLINE
ACCESSION NUMBER: 95254592 MEDLINE
DOCUMENT NUMBER: 95254592
TITLE: ***Fusion*** ***protein*** mediated ***prodrug*** activation (FMPA) in vivo.
AUTHOR: Bosslet K; Czech J; Seemann G; Monneret C; Hoffmann D
CORPORATE SOURCE: Research Laboratories of Behringwerke AG, Marburg, Germany..
SOURCE: CELL BIOPHYSICS, (1994) 24-25 51-63.
Journal code: CQC. ISSN: 0163-4992.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
AB A two component system, consisting of a ***fusion*** ***protein*** and an appropriate ***prodrug*** , suited to perform selective tumor therapy in vivo, is presented. The ***fusion*** ***protein*** , owing to its humanized ***carcinoembryonic*** antigen (***CEA***)-specific variable region, specifically binds to ***CEA*** -expressing tumors and has an enzymatic activity comparable to human beta-glucuronidase. The ***prodrug*** is a nontoxic glucuronide-spacer-derivative of doxorubicin decomposing to doxorubicin by enzymatic deglucuronidation. In vivo studies in nude mice bearing human ***CEA*** -expressing tumor xenografts revealed that 7 d after injection of 20 mg/kg ***fusion*** ***protein*** , a high specificity ratio (> 100:1) was obtained between tumor and plasma. Injection of 250 mg/kg of ***prodrug*** at d 7 resulted in tumor therapeutic effects superior

to
conventional chemotherapy without any detectable toxicity. These superior therapeutic effects that were observed using established human tumor xenografts can be explained by the approx 10-fold higher drug concentrations found in tumors of mice treated with ***fusion*** ***protein*** and ***prodrug*** than in those treated with the maximal tolerable dose of drug alone.

L33 ANSWER 72 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:430072 CAPLUS
DOCUMENT NUMBER: 121:30072
TITLE: Pretargeting methods and compounds, including radiolabeled biotins
INVENTOR(S): Axworthy, Donald B.; Theodore, Louis J.; Gustavson, Linda M.; Reno, John M.
PATENT ASSIGNEE(S): Neorx Corp., USA
SOURCE: PCT Int. Appl., 198 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9325240	A2	19931223	WO 1993-US5406	19930607
WO 9325240	A3	19940217		
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5283342	A	19940201	US 1992-895588	19920609
EP 646019	A1	19950405	EP 1993-915235	19930607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07507804	T2	19950831	JP 1993-501638	19930607
US 6022966	A	20000208	US 1993-156565	19931122
US 5911969	A	19990615	US 1994-329617	19941026
US 6075010	A	20000613	US 1994-350551	19941207
US 5608060	A	19970304	US 1995-351469	19950221
US 5976535	A	19991102	US 1995-468513	19950606
US 6015897	A	20000118	US 1996-645211	19960513
PRIORITY APPLN. INFO.:			US 1992-895588	19920609
			US 1992-995381	19921223
			US 1992-995383	19921223
			WO 1993-US5406	19930607
			US 1993-163184	19931207
			US 1993-163188	19931207
			US 1994-351005	19941207

OTHER SOURCE(S): MARPAT 121:30072
AB Methods, compds., compns. and kits related to pretargeted delivery (for improved ***targeting*** ratio or increased abs. dose to the ***target*** cell site, in comparison to conventional cancer ***therapy***) of diagnostic and ***therapeutic*** agents are disclosed. In particular, methods for radiometal labeling of biotin (biotin chelates) and for improved radiohalogenation of biotin, as well as
related compds., are described. Clearing agents, anti-ligand-***targeting*** moiety conjugates, ***target*** cell retention enhancing moieties and addnl. methods are discussed. Thus, in a three-step pretargeting protocol involving sequential administration (at 0, 24, and 26 h, resp.) of (125I-labeled) biotinylated antibody

(NR-LU-10), (131I-labeled) avidin, and a 186Re chelate-biotin conjugate (prepn. given) to tumor-bearing mice, the biotin-chelate conjugate reached a peak in the tumor approx. 7 times greater than that obsd. in the absence of biotinylated antibody and avidin. The specifically bound biotin-chelate conjugate was retained at the tumor at significant levels for >50 h. Prepn. of biotin-chelate conjugates having improved biodistribution properties, radioiodinated biotin derivs., DOTA-biotin conjugates, clearing agents, etc. is also described.

L33 ANSWER 73 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:669007 CAPLUS
DOCUMENT NUMBER: 119:269007
TITLE: Cellular immunity vaccines from bacterial toxin-antigen conjugates
INVENTOR(S): Donnelly, John J.; Liu, Margaret A.; Friedman, Arthur; Montgomery, Donna L.; Hawe, Linda A.; Oliff, Allen I.; Shi, Xiao Ping; Ulmer, Jeffrey; Marshall, Mark S.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 85 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 532090	A2	19930317	EP 1992-202660	19920902
EP 532090	A3	19941228		
R: CH, DE, FR, GB, IT, LI, NL				
CA 2077277	AA	19930310	CA 1992-2077277	19920901
JP 05345800	A2	19931227	JP 1992-240293	19920909
PRIORITY APPLN. INFO.:			US 1991-756249	19910909

AB Recombinant hybrid proteins having 2 primary components are disclosed in which the 1st component is a modified bacterial toxin that has translocating ability and the 2nd component is a polypeptide or protein that is exogenous to an antigen-presenting cell (APC). The hybrid has the ability to be internalized by an APC, where the hybrid is subsequently processed and an antigenic segment of the hybrid presented on the surface of the APC, where the segment elicits an immune response by cytotoxic T-lymphocytes (CTL). Thus, an influenza virus Ma sequence (coding for residues 57-68 of the influenza matrix protein) was produced and subcloned into construct BS-PE (contg. domain I and II coding regions of Pseudomonas exotoxin) to give plasmid BS-PEMa-1. In an assay for CTL cytotoxicity against U-2 OS cells incubated with 51Cr and PEMa protein, the percent specific lysis was in the 60-65% range, compared to 85-90% range for the pos. control and >5% range for neg. controls. Other data suggested that the ability of PEMa to sensitize ***target*** cells for lysis by CTL specific for the matrix peptide is mediated through Pseudomonas exotoxin receptor-mediated uptake and processing. Generation of other constructs is described, and nucleotide and amino acid sequences are included.

L33 ANSWER 74 OF 82 MEDLINE

ACCESSION NUMBER: 95102760 MEDLINE
DOCUMENT NUMBER: 95102760
TITLE: Recombinant bifunctional molecule FV/IFN-gamma possesses the anti-tumor FV as well as the gamma interferon activities.
AUTHOR: Xiang J; Qi Y; Luo X; Liu E
CORPORATE SOURCE: Saskatoon Cancer Center, Department of Microbiology, University of Saskatchewan, Canada.
SOURCE: CANCER BIOTHERAPY, (1993 Winter) 8 (4) 327-37.
Journal code: BTN. ISSN: 1062-8401.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504

AB Recombinant DNA techniques were used to clone, construct and express the bifunctional molecule FV/IFN-gamma. The FV/IFN-gamma is a single-chain 42KD ***fusion*** ***protein*** expressed in E. coli under control of the strong T7 bacteriophage promoter in the expression vector pT7-7-FV-IFN-gamma. The fused gene fragment FV-IFN-gamma containing a single-chain anti-TAG72 FV gene fragment as well as the human recombinant cDNA fragment of IFN-gamma molecule. The renatured soluble form of FV/IFN-gamma was purified from E. coli inclusion bodies using HTPT chromatography. The yield of this ***fusion*** ***protein*** was estimated at 10mg/L. Our data showed that the FV/IFN-gamma molecule retained the TAG72 antigen-binding specificity and the IFN-gamma activity as measured in ELISA, Western blotting and up-regulation of ***CEA*** expression by IFN-gamma. Therefore, it may prove to be useful in ***targeting*** the biological effect of IFN-gamma to tumor cells and stimulating its immune destruction.

L33 ANSWER 75 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:508496 CAPLUS
DOCUMENT NUMBER: 119:108496
TITLE: Molecular and functional characterization of a ***fusion*** ***protein*** suited for tumor specific ***prodrug*** activation
AUTHOR(S): Bosslet, K.; Czech, J.; Lorenz, P.; Sedlacek, H. H.; Schuermann, M.; Seemann, G.
CORPORATE SOURCE: Behring Res. Lab., Marburg, W-3550, Germany
SOURCE: Monoclonal Antibodies 2 (1993), 205-17. Editor(s): Epenetos, Agamemnon A. Chapman and Hall: London, Uk. CODEN: 59CLAZ
DOCUMENT TYPE: Conference
LANGUAGE: English

AB This study demonstrates that a mol. construct consisting essentially of the binding region of the humanized anti- ***CEA*** mAb 431 and the human endogenous lysosomal enzyme .beta.-glucuronidase could be expressed and purified to homogeneity as a highly effective ***fusion*** ***protein*** . Using the ***fusion*** ***protein*** activity assay the authors were able to detect eight BHK transfectomas secreting significant amts. of ***fusion*** ***protein*** that bind to ***CEA*** and catalyze the cleavage of the 4-methylumbelliferyl .beta.-glucuronide ***prodrug*** to 4-methylumbelliferone and glucuronic acid due to the ***fusion*** ***protein*** 's .beta.-glucuronidase activity. From transfectoma supernatants two mols. could be isolated using anti-idiotype affinity chromatog. Under denaturing conditions one mol. represented a monovalent protein, the other

consisted of a bivalent protein as revealed by SDS-PAGE and Western blotting data. The monovalent mol. (mol. wt 125) contains the light chain of the humanized mAb BW 431 consisting of the VL and CL domains covalently linked by an interchain disulfide bond to the humanized heavy chain. The humanized heavy chain is built up of the VH and CH1 domain of the humanized mAb BW 431, the N-terminal part of the human IgG3 hinge region, a linker peptide and the human .beta.-glucuronidase. In this monovalent mol. the two hinge region cysteines form an intrachain disulfide bond. If the hinge region cysteines form two interchain disulfide bonds a bivalent ***fusion*** ***protein*** arises which can be isolated from transfectoma supernatants in a similar amt. as the monovalent ***fusion*** ***protein*** . Under native conditions the two mol. forms exist as bivalent mols. as shown by gel chromatog. under non-denaturing conditions. This is the first report describing a functionally active ***fusion*** ***protein*** which consists of a humanized tumor-selective binding portion and a human lysosomal enzyme with potential applicability for a more selective tumor therapy.

L33 ANSWER 76 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:605187 CAPLUS
DOCUMENT NUMBER: 117:205187
TITLE: cell surface receptor- ***targeted*** molecules for the ***treatment*** of viral diseases
INVENTOR(S): Nichols, Jean C.
PATENT ASSIGNEE(S): Seragen, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9215318	A1	19920917	WO 1992-US1705	19920305
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
AU 9216436	A1	19921006	AU 1992-16436	19920305
JP 06508821	T2	19941006	JP 1992-508253	19920305
EP 721340	A1	19960717	EP 1992-908403	19920305
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
NO 9303171	A	19931111	NO 1993-3171	19930906
US 6074636	A	20000613	US 1995-465541	19950605
AU 9660873	A1	19961031	AU 1996-60873	19960730
AU 705327	B2	19990520		
AU 9940160	A1	19990916	AU 1999-40160	19990716
PRIORITY APPLN. INFO.:			US 1991-665762	19910307
			WO 1992-US1705	19920305
			US 1992-914492	19920715
			US 1993-53557	19930427
			US 1994-289128	19940811
			AU 1996-60873	19960730

AB A viral infection is ***treated*** by administration of a mol.

capable
of specifically binding to a proteinaceous receptor (e.g. the high-affinity interleukin-2 receptor) on a cell which contributes to the pathol. of the viral infection; this mol. is covalently bound to (or a hybrid with) a mol. capable of decreasing cell viability, such as a cytotoxin. Thus, DAB486IL-2, a ***fusion*** ***protein*** in which the receptor-binding domain of diphtheria toxin is replaced by a portion of human IL-2, killed T-cells infected with human immunodeficiency virus 1 (HIV-1), selectively eliminated HIV-1-infected cells from mixed cultures of infected and uninfected T-cells, and reduced HIV-1 replication in cultures of infected monocytes. DAB486IL-2 also inhibited prodn. of viral proteins and blocked prodn. of ***infectious*** HIV-1 in cultures of infected T-cells.

L33 ANSWER 77 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:66829 CAPLUS
DOCUMENT NUMBER: 118:66829
TITLE: Fusion proteins of monoclonal antibodies and .beta.-glucuronidase for site-specific ***prodrug*** activation
INVENTOR(S): Seemann, Gerhard; Bosslet, Klaus; Czech, Joerg; Kolar, Cenek; Hoffmann, Dieter; Sedlacek, Hans Harald
PATENT ASSIGNEE(S): Behringwerke A.-G., Germany
SOURCE: Eur. Pat. Appl., 34 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 501215	A2	19920902	EP 1992-102197	19920210
EP 501215	A3	19930811		
EP 501215	B1	20000524		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
DE 4106389	A1	19920903	DE 1991-4106389	19910228
AU 9211251	A1	19930128	AU 1992-11251	19920227
AU 660445	B2	19950629		
CA 2062047	AA	19920829	CA 1992-2062047	19920228
JP 07179500	A2	19950718	JP 1992-78644	19920228
PRIORITY APPLN. INFO.:			DE 1991-4106389	19910228

AB Fusion proteins of humanized or human-specific monoclonal antibodies and .beta.-glucoronidase are prepd. for use in the activation of glucuronides of neoplasm inhibitors at the tumor site. The enzyme is significantly more active when it is linked to the V-region of the antibody via a linker peptide. Preferred antibodies are human IgG3. A gene for a ***fusion*** ***protein*** of a humanized antibody to an epitope of ***carcinoembryonic*** antigen (***CEA***) and a .beta.-glucuronidase was constructed and introduced into BHK cells. The resulting protein had the binding specificity of the antibody and the activity of the enzyme was shown by antigen binding assays. Specificity was further demonstrated by competition assays with the murine antibody from which the variable regions were derived. When used in an in vivo

test (human ***CEA*** -pos. tumor in nude mice) it was found that the protein was rapidly lost from non- ***target*** tissues (>98% loss within 216 h after final administration) and retained by the tumor (.apprx.25% retention 216 h after final administration). The ability of the ***fusion*** ***protein*** to cleave the glucuronide of a daunurobicin deriv. (***prodrug***) is demonstrated.

L33 ANSWER 78 OF 82 MEDLINE
ACCESSION NUMBER: 92153684 MEDLINE
DOCUMENT NUMBER: 92153684
TITLE: Molecular and functional characterisation of a ***fusion*** ***protein*** suited for tumour specific ***prodrug*** activation.
AUTHOR: Bosslet K; Czech J; Lorenz P; Sedlacek H H; Schuermann M; Seemann G
CORPORATE SOURCE: Research Laboratory of Behringwerke, Marburg, Germany..
SOURCE: BRITISH JOURNAL OF CANCER, (1992 Feb) 65 (2) 234-8. Journal code: AV4. ISSN: 0007-0920.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199205
AB A ***fusion*** ***protein*** consisting of the humanised Fab fragment of the anti ***CEA*** MAb BW 431 and the human beta-glucuronidase was expressed in BHK cells. Functional testing revealed that the specificity and avidity of the humanised V region was similar to the original murine MAb BW 431. Furthermore, the enzymatic activity, pH sensitivity and stability of the human beta-glucuronidase in the ***fusion*** ***protein*** was comparable to the activity of recombinant human beta-glucuronidase. Using anti-idiotype affinity chromatography, two molecules of a molecular weight of 125 kDa or 250 kDa could be visualized under nonreducing conditions in SDS-PAGE. Reducing conditions revealed a 25 kDa light and 100 kDa heavy chain. Due to its suitable biological characteristics this ***fusion*** ***protein*** might be an appropriate molecule allowing a site specific antibody directed enzyme ***prodrug*** therapy (***ADEPT***) in vivo.

L33 ANSWER 79 OF 82 MEDLINE
ACCESSION NUMBER: 93024517 MEDLINE
DOCUMENT NUMBER: 93024517
TITLE: Colorimetric detection of Plasmodium falciparum and direct sequencing of amplified gene fragments using a solid phase method.
AUTHOR: Holmberg M; Wahlberg J; Lundeberg J; Pettersson U; Uhlen M
CORPORATE SOURCE: Department of Medical Genetics, Biomedical Center, Uppsala, Sweden.
SOURCE: MOLECULAR AND CELLULAR PROBES, (1992 Jun) 6 (3) 201-8. Journal code: NG9. ISSN: 0890-8508.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
AB A rapid colorimetric assay for the detection of DNA from Plasmodium falciparum malaria is described, allowing direct sequencing of amplified fragments in the positive samples. The method is based on amplification

by
the polymerase chain reaction (PCR), with incorporation of biotin and a lac operator sequence in the amplified ***target*** DNA. The PCR product was immobilized on streptavidin-coupled magnetic beads, and detected by the specific binding of an Escherichia coli lac repressor beta-galactosidase ***fusion*** ***protein*** . Positive samples were subsequently ***treated*** with alkali to generate single stranded templates, which were used for solid phase genomic sequencing. As
targets for amplification and sequencing we selected a region of
the gene for the antigen Pf155/RESA and a region of the ***parasite*** dihydrofolate reductase gene (PfDHFR/TS). We show here that both of these gene ***targets*** can be used for specific detection of P. falciparum
in patient blood samples. Genomic sequencing of five patient isolates revealed no variation in the Pf155/RESA gene fragment. In a comparison of this sequence with conserved protein domains, a marked similarity to the src homology region 3 was detected. A point mutation was found in the PfDHFR/TS gene fragment of one of the clinical samples, replacing Ser108 with Asn. This mutation has earlier been described in pyrimethamine and cycloguanile-resistant strains of P. falciparum.

L33 ANSWER 80 OF 82 MEDLINE
ACCESSION NUMBER: 91168164 MEDLINE
DOCUMENT NUMBER: 91168164
TITLE: Preparation of synthetic polypeptide domains of ***carcinoembryonic*** antigen and their use in epitope mapping.
AUTHOR: Hass G M; Bolling T J; Kinders R J; Henslee J G; Mandecki W; Dorwin S A; Shively J E
CORPORATE SOURCE: Abbott Laboratories, Abbott Diagnostics Division, Abbott Park, Illinois 60064..
SOURCE: CANCER RESEARCH, (1991 Apr 1) 51 (7) 1876-82.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199106
AB Genes encoding the four principal polypeptide domains (N, A1-B1, A2-B2, and A3-B3) of ***carcinoembryonic*** antigen (***CEA***) were synthesized and expressed in Escherichia coli as fusion products with bacterial CMP-KDO synthetase (CKS). The four synthetic fusion proteins were purified in high yield and used as ***targets*** in Western blots
for 11 anti- ***CEA*** MAbs and to compete with immobilized ***CEA***
for binding to four of these MAbs. Each of the MAbs showed strong binding to one or more of the fusion proteins. In Western blots, MAbs H19C91 and 4230 bound only to CKS-N. MAbs H8C2 and H11C35 bound only CKS-A1-B1, and MAbs T84.66, H46C136, and H21C83 appeared to be specific for CKS-A3-B3. None of the MAbs tested bound only to CKS-A2-B2. However, two MAbs bound both CKS-A1-B1 and CKS-A3-B3 and one MAb (3519) bound to all three of the repeated domains. Since these three domains exhibit over 90% amino acid sequence homology, the latter results were not surprising. The competition
studies largely confirmed the results of Western blots but did show some MAb- ***fusion*** ***protein*** interactions not observed in Western blots. These competition studies also allowed estimation of the

relative affinities of the MAbs for the synthetic domains and for native ***CEA*** . These studies demonstrated that epitopes in ***CEA*** recognized by the MAbs in this study are peptide in nature and that the fusion proteins are of utility in the localization of the epitopes on the polypeptide chain of ***CEA*** .

L33 ANSWER 81 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1991:97531 CAPLUS
DOCUMENT NUMBER: 114:97531
TITLE: Chimeric proteins incorporating a metal binding protein, their labeling, and their use in diagnosis and ***therapy***
INVENTOR(S): Shoemaker, Hubert J. P.; Ghrayeb, John; Sun, Lee K.
PATENT ASSIGNEE(S): Centocor, Inc., USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9006323	A1	19900614	WO 1989-US5424	19891129
WO 9006323	A3	19900712		
WO 9006323	A2	19900614		

W: JP
RW: AT, BE, CH, DE, ES, FR, GB, IT, LU, NL, SE
PRIORITY APPLN. INFO.: US 1988-277330 19881129
AB A chimeric protein comprises a protein having an affinity for a biol. ***target*** linked through a peptide bond to a metal-binding protein or functional domain thereof to form a contiguous polypeptide. The chimeric protein may be stably labeled with a metal, preferably a radiometal, for diagnostic and ***therapeutic*** procedures. Plasmid phC.gamma. (contg. the human C.gamma.4 genomic DNA), plasmid phMTII-3 (a cDNA clone of human metallothionein), and the functionally rearranged heavy chain variable gene of Ig 17-1A were used to construct the expression vector pSV2.DELTA.Hgpt17-1AVHhC.gamma.4MT. The resulting Ig heavy chain-metallothionein chimeric construct was transfected into mouse myeloma Sp2/0 cells producing Ig17-1A light chain, and cell line G4K/MT producing chimeric antibody IgG4K/MT was selected. The antibody was labeled with 99mTc by warming to 37.degree. in the presence of 99mTc glucarate. The labeled antibody bound to HT29 human colorectal carcinoma cells in the presence of purified IgG17-1A or G4K/MT.

L33 ANSWER 82 OF 82 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1989:3839 CAPLUS
DOCUMENT NUMBER: 110:3839
TITLE: ***Targeted*** system for administering ***therapeutic*** or radiodiagnostic compounds, involving biotinylated agent, avidin-containing binding protein, and a ***clearing*** ***agent*** , especially for use with tumors
INVENTOR(S): Goodwin, David A.; Meares, Claude; McCall, Michael
PATENT ASSIGNEE(S): Leland Stanford Junior University, USA
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 251494	A2	19880107	EP 1987-304796	19870529
EP 251494	A3	19900110		
EP 251494	B1	19920930		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4863713	A	19890905	US 1986-877327	19860623
JP 63005033	A2	19880111	JP 1986-236984	19861003
AT 81018	E	19921015	AT 1987-304796	19870529
PRIORITY APPLN. INFO.:			US 1986-877327	19860623
			EP 1987-304796	19870529

AB Substances involved in administering a diagnostic or ***therapeutic*** agent to internal ***target*** sites are: a) a biotinylated compd. contg. the diagnostic or ***therapeutic*** agent; b) an avidin-contg. binding protein capable of localizing selectively at the ***target*** tissue when administered parenterally; and c) a ***clearing*** ***agent*** capable of reacting with the binding protein when circulating in the bloodstream of to form a macromol. aggregate which is cleared by the reticuloendothelial system. Biotin was coupled to p-isothiocyanto-EDTA through a putrescin spacer, and ***treated*** with 111In to give a chelated complex (I). Mice with KHJJ tumors were pretargeted with 0.25 nmol streptavidin i.v., and ***treated*** i.v. with biotinylated human transferrin, at 20 h, and 0.016 nmol I, at 21 h. Three h after I administration, the tumor 111In level was 0.45% dose/g, with a tumor blood ratio of about 4.74; when the biotinylated transferrin was not given at 20 h, the tumor/blood ratio was about 1.52. Thus good tumor ***targeting*** can be achieved by chelating binding to prelocalized streptavidin, and the removal of blood streptavidin by a chase compd. significantly reduces 111In background due to blood levels of the bound 111In complex.

L13 ANSWER 25 OF 29 MEDLINE DUPLICATE 10

ACCESSION NUMBER: 96427936 MEDLINE
DOCUMENT NUMBER: 96427936 PubMed ID: 8965250
TITLE: [***Camptothecin*** and derivatives: a new class of antitumor agents].
Camptothecine et derives: une nouvelle classe d'agents antitumoraux.
AUTHOR: Torck M; Pinkas M
CORPORATE SOURCE: Laboratoire de Pharmacognosie, Faculte des Sciences Pharmaceutiques et Biologiques, Lille, France.
SOURCE: JOURNAL DE PHARMACIE DE BELGIQUE, (1996 Jul-Aug) 51 (4) 200-7. Ref: 82
Journal code: JNB; 0375351. ISSN: 0047-2166.
PUB. COUNTRY: Belgium
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961205

AB ***Camptothecin*** (CPT), an alkaloid isolated from the stem wood and bark of Camptotheca acuminata native to China, was discovered in the early 60's after a systematic screening of natural products by the National Cancer Institute (NCI). This new anticancer agent displays an unique mechanism of action as it inhibits intranuclear enzyme topoisomerase 1, involved in DNA replication. CPT is poorly water ***soluble*** and causes severe and unpredictable toxicities such as haemorrhagic cystitis and diarrhea; for therefore reason, a number of analogues have been synthetized in a attempt to define the features of the molecule that are essential for cytotoxicity and to produce derivatives with increased ***solubility*** . Clinical trials of several ***soluble*** molecules are in progress in the different countries: irinotecan, topotecan, 9-AC. Encouraging results are observed against solid tumors. Irinotecan was recently commercialized in France. It is a ***prodrug*** ; the active metabolite SN-38 showed a good activity in metastatic colorectal adenocarcinoma; the limiting toxicities are myelotoxicity and essentially late diarrhea. However, new studies are needed for state precisely the optimal schedule of administration and association with other chemotherapeutic agents.

L9 ANSWER 2 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999045203 MEDLINE
DOCUMENT NUMBER: 99045203
TITLE: Irinotecan (***CPT*** - ***11***) metabolism and disposition in cancer patients.
AUTHOR: Sparreboom A; de Jonge M J; de Bruijn P; Brouwer E; Nooter K; Loos W J; van Alphen R J; Mathijssen R H; Stoter G; Verweij J
CORPORATE SOURCE: Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, The Netherlands.. sparreboom@onch.azr.nl
SOURCE: CLINICAL CANCER RESEARCH, (1998 Nov) 4 (11) 2747-54. Journal code: C2H. ISSN: 1078-0432.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY WEEK: 19990404
AB The objective of this study was to determine the metabolic fate and disposition of the antitumor camptothecine derivative irinotecan (***CPT*** - ***11***). Ten patients with histological proof of malignant solid tumor received 200 mg/m2 ***CPT*** - ***11*** as a 90-min i.v. infusion, followed by a 1.5-h i.v. infusion of cisplatin (60 or 80 mg/m2). Plasma, urine, and feces were collected for 56 h and analyzed by a specific reversed-phase high-performance liquid chromatographic assay for the parent drug and all four metabolites positively identified to date: SN-38; its beta-glucuronide ***conjugate*** , SN-38 beta-glucoronide (SN-38G); 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecine (APC); and 7-ethyl-10-[4-N-(1-piperidino)-1-amino]-carbonyloxycamptothecine (NPC). A three-exponential decline was observed in plasma for all compounds, with a clear predominance of the parent drug [25.6+/-5.71 microM x h (***CPT*** - ***11***) versus 15.8+/-3.51 microM x h (total metabolites)]. Total urinary excretion was 28.1+/-10.6% of the dose, with unchanged ***CPT*** - ***11*** and SN-38G as the main excretion products. Whereas renal clearance of SN-38 was only a minor route of drug elimination, fecal concentrations of this compound were unexpectedly high (on average, 2.45% of the dose), suggestive of intestinal hydrolysis of SN-38G by bacterial beta- ***glucuronidase*** . ***CPT*** - ***11*** and the other metabolites could also be identified from fecal extracts, with a very minor contribution overall of the cytochrome P-450-mediated compounds 7-ethyl-10-[4-N-(1-piperidino)-1-amino]-carbonyloxycamptothecine and 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecine. Surprisingly, fecal excretion accounted for only 24.4+/-13.3% of the dose, leading to a total excretion of approximately 52%. These data indicate that half of the dose in urine and feces may constitute some further unknown nonextractable or nonfluorescent metabolites. The findings from this study should be of importance as a guide to further therapeutic evaluation of this drug.

L9 ANSWER 3 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998394152 MEDLINE

DOCUMENT NUMBER: 98394152
TITLE: Pharmacology of irinotecan.
AUTHOR: Kuhn J G
CORPORATE SOURCE: College of Pharmacy, University of Texas at Austin, USA.
SOURCE: ONCOLOGY, (1998 Aug) 12 (8 Suppl 6) 39-42. Ref: 16
Journal code: AVP. ISSN: 0890-9091.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY WEEK: 19990303

AB Irinotecan (***CPT*** - ***11*** [Camptosar]), a semisynthetic derivative of the plant alkaloid camptothecin, is bioactivated by carboxylesterases (EC3.1.1-) to the topoisomerase I inhibitor SN-38, a minor metabolite. Bioactivation of intravenously administered irinotecan by carboxylesterases occurs predominantly in the liver. Two human carboxylesterase isoforms responsible for SN-38 formation have been characterized. At relevant hepatic irinotecan concentrations up to 12 micrograms/mL, a low-Km isoform is responsible for irinotecan bioactivation. High concentrations of drugs commonly coadministered with irinotecan do not inhibit carboxylesterase activity. Intestinal carboxylesterases can also generate SN-38, followed by subsequent oral absorption. A second major polar metabolite of irinotecan, aminopentanecarboxylic acid (APC), is the product of CYP3A4-mediated oxidation of the terminal piperidine ring. APC is 100-fold less active than SN-38 as a topoisomerase I inhibitor and is a relatively weak inhibitor of acetylcholinesterase. SN-38 is eliminated mainly through conjugation by hepatic uridine glucuronosyltransferase (UGT*1.1), the same isoezyme responsible for glucuronidation of bilirubin. Grade 4 irinotecan-related toxicity (ie, neutropenia, diarrhea) has recently been reported in two patients with deficient UGT*1.1 activity. SN-38 glucuronide (SN-38G), which has only 1/100th the antitumor activity of SN-38, is actively secreted into the bile by a canalicular ***multispecific*** organic anion transporter. Deconjugation of SN-38G to SN-38 by beta- ***glucuronidase*** produced by the intestinal flora may contribute to enterohepatic recirculation of SN-38 and delayed intestinal toxicity.

L9 ANSWER 4 OF 4 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 96328099 MEDLINE
DOCUMENT NUMBER: 96328099
TITLE: Involvement of beta- ***glucuronidase*** in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride (***CPT*** - ***11***) in rats.
AUTHOR: Takasuna K; Hagiwara T; Hirohashi M; Kato M; Nomura M; Nagai E; Yokoi T; Kamataki T
CORPORATE SOURCE: Drug Safety Research Laboratory, Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan.
SOURCE: CANCER RESEARCH, (1996 Aug 15) 56 (16) 3752-7.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199611

AB Irinotecan hydrochloride (***CPT*** - ***11***), an antitumor camptothecin derivative, causes severe forms of diarrhea clinically. We characterized ***CPT*** - ***11*** -induced diarrhea histologically and enzymologically and assessed the relationships between intestinal toxicity and the activity of the enzymes that play a key role in the major metabolic pathway of ***CPT*** - ***11*** in rats. ***CPT*** - ***11*** (60 mg/kg i.v. for 4 days) induced intestinal toxicity characterized by severe chronic diarrhea, loss of body weight, and anorexia. Histological damage was most severe in the cecum. The segmental difference in the degree of the damage showed good correlation with the beta- ***glucuronidase*** activity in the contents of the lumen in each case, but not with the intestinal tissue carboxylesterase activity, which converts ***CPT*** - ***11*** to its active form (7-ethyl-10-hydroxycamptothecin). Inhibition of the beta- ***glucuronidase*** activity in the intestinal microflora by antibiotics (1 mg penicillin and 2 mg streptomycin per ml of drinking water) markedly ameliorated the diarrhea and reduced cecal damage. Analysis of ***CPT*** - ***11*** and its metabolites in the feces indicated that antibiotics completely inhibited the deconjugation of the glucuronic ***conjugate*** of 7-ethyl-10-hydroxycamptothecin by beta- ***glucuronidase*** . It is suggested that ***CPT*** - ***11*** -induced diarrhea would be attributable to the damage to the cecum, and that the inhibition of the beta- ***glucuronidase*** activity in the intestinal microflora is a major protective effect of antibiotics.

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L7 ANSWER 35 OF 36 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94141396 EMBASE
DN 1994141396
TI Tumor-selective **prodrug** activation by **fusion protein**-mediated catalysis.
AU Bosslet K.; Czech J.; Hoffmann D.
CS Res. Laboratories of Behringwerke AG, P. O. Box 11 40,D-35001 Marburg, Germany
SO Cancer Research, (1994) 54/8 (2151-2159).
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB A two component system, consisting of a **fusion protein** and an appropriate **prodrug**, suited to perform selective tumor therapy in vivo is presented. The **fusion protein**, due to its humanized carcinoembryonic antigen-specific variable region, specifically binds to carcinoembryonic antigen-expressing tumors and has an **enzymatic** activity comparable to that of human .beta.-glucuronidase. The **prodrug** is a nontoxic glucuronide-spacer derivative of doxorubicin decomposing to doxorubicin by **enzymatic** deglucuronidation. In vivo studies in nude mice bearing human carcinoembryonic antigen-expressing tumor xenografts revealed that 7 days after injection of 20 mg/kg **fusion protein** a high specificity ratio (>100:1) was obtained between tumor and plasma or tumor and normal tissues. Injection of 250 mg/kg of **prodrug** at day 7 resulted in tumor therapeutic effects superior to those of conventional chemotherapy without any detectable toxicity. These superior therapeutic effects which were observed using established human tumor xenografts can be explained by the approximately 4-12-fold higher doxorubicin concentrations found in tumors of mice treated with **fusion protein** and **prodrug** than in those treated with the maximal tolerable dose of drug alone. The nondetectable toxicity in the animals treated with **fusion protein** and **prodrug** is probably caused by up to 5-fold lower drug concentrations in normal tissues compared to the animals treated with doxorubicin. Thus, a more tumor-selective therapy, resulting in stronger therapeutic effects and reduced toxicity seems to be possible by the appropriate use of the humanized nontoxic **fusion protein** and the nontoxic **prodrug**.
CT Medical Descriptors:
*drug activation
*drug selectivity
animal experiment
animal model
animal tissue
article
controlled study
dose response
drug distribution
drug stability
drug targeting
drug tissue level
enzyme activity
female
immunohistochemistry
intravenous drug administration

monkey
mouse
nonhuman
priority journal
protein binding
rat
tissue specificity
tumor growth
Drug Descriptors:
*doxorubicin derivative: CB, drug combination
*doxorubicin derivative: DV, drug development
*doxorubicin derivative: PK, pharmacokinetics
*hybrid protein: CB, drug combination
*hybrid protein: DV, drug development
***prodrug: CB, drug combination**
***prodrug: DV, drug development**
***prodrug: PK, pharmacokinetics**
beta glucuronidase
carcinoembryonic antigen
RN (beta glucuronidase) 9001-45-0